POLYSOMNOGRAPHY IN CHILDREN WITH BREATH HOLDING SPELLS

Omneya Gamal El din Afify[1], Mona El Falaky[1], Nevine Ramzy El-Baroudy[1], Radwa M. Azmy[2], Basma Bahgat El Sayed[2], Nour Elkhateb[1], Nesma Ahmed Fouad Mubarak[1*]

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Abstract

Background: Breath holding spells (BHS) are known as paroxysmal benign non-epileptic disorders. BHS have been reported in 0.1–4.6% of children in Western countries. Polysomnography (PSG) is a reliable, non-invasive tool used to study sleep architecture.
Objectives: to investigate the possibility that children with BHS may demonstrate sleep-disordered breathing (SDB) during PSG, in addition to assessment of the relation between characteristics of BHS, and iron deficiency anemia and EEG abnormality in our study group.
Methods: In our study, thirty children diagnosed of BHS 18 males and 12 females, were enrolled from the Neuropediatric Outpatient Clinic, Cairo University Children Hospital (CUCH).
Results: Results revealed that 50% of our patients had central sleep apnea however obstructive sleep apnea was not present. There was a statistically significant inverse correlation between the severity of BHS in our patients and their hemoglobin levels. Also, there was a statistically significant relation between severity of BHS and lowest oxygen saturation measured during PSG. There was a statistically significant positive correlation between frequency of BHS in our patients and sleeping difficulties determined by ISQ, showing that patients with sleeping difficulties according to ISQ2 had experienced higher frequency of BHS. There was a statistically significant moderate, negative association between frequency of BHS and EEG abnormality.
Conclusion: We concluded that BHS are more frequent and more severe with children suffering of sleeping difficulties, iron deficiency anemia or EEG abnormalities.

Keywords: breath holding spells, sleep disordered breathing, polysomnography

[1]Department of Pediatrics and Pediatric Neurology, Faculty of Medicine Cairo University, Egypt.
[2]Department of Neurophysiology, Faculty of Medicine Cairo University, Egypt.
[*]Corresponding email: nesmamubarak55@gmail.com

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1. INTRODUCTION

Breath holding spells (BHS) are benign non-epileptic paroxysmal events, but can be frightening to parents. The term BHS is a misnomer and implies that the child is voluntarily holding his or her breath in a prolonged inspiration, whatever episodes actually occur during expiration and is involuntary[1].
Breath holding spells are not uncommon affecting 4.7% of children, the typical age of onset is between 6 and 18 months and are provoked by a painful, frightening, or irritating event and usually lasts for less than one minute[2].
Iron deficiency anemia is commonly found in these children with BHS and iron therapy usually improves the condition[3].
The BHS are classified by the color change during the event into cyanotic or pallid spells. The more common cyanotic form is considered to be due to inhibition of respiratory effort due to autonomic instability, or intra-pulmonary shunting as a result of abnormal pulmonary reflexes[4].
Children with BHS may demonstrate sleep-disordered breathing (SDB) during polysomnography (sleep laboratory), independent treatment of SDB may hasten resolution of spells[5].
Markers of sleep architecture and sleep state can be objectively and non-invasively measured and referenced to developmental norms. Polysomnography is a reliable, non-invasive tool used to study the basic mechanisms of sleep and has proven useful to neuropsychiatric medicine by serving to identify trait markers for various diseases[6].

2. PATIENTS AND METHODS

This was a descriptive cross-sectional hospital- based study, conducted on a cohort of thirty children diagnosed of having breath holding spells, who attended the Neuropediatric Outpatient Clinic, Cairo

University Children Hospital (CUCH), in the time period between January 2017 and December 2018.

Patients' ages ranged from 9 - 48 months old, 18 of them were males and 12 were females.

The present study was conducted on thirty children diagnosed with breath holding spells (BHS), recruited from the Neuropediatric Outpatient Clinic, Cairo University Children Hospital (CUCH) in the time period between January 2017 and December 2018.

Written informed consents were obtained from care givers to enroll their children in the study. The study protocol was approved by ethical committee of Cairo University.

- **Inclusion criteria**

Thirty children presenting with breath holding spells (BHS) during the study were included, they fulfilled the following criteria: The diagnosis of BHS was done clinically by a pediatric neurologist based on the history given by the child's care giver and exclusion of other causes of spells. A "spell" is defined as stoppage of child's breathing during expiration after a deep inspiration while crying. The spells were classified into cyanotic or pallid spells (**Swaiman et al., 2011**)[1] and Patients' ages ranged from 6 months to 60 months old at the time of the study.

- **Exclusion criteria**

Patients were excluded from the study if they had any of these criteria: Patients with history of febrile convulsions or epilepsy, current treatment with anticonvulsant medications or a clinically identified mental disability, Patients of age more than 5 years and Patients with history of bronchial asthma, recurrent bronchiolitis, frequent tonsillitis, adenoids or any cardiac diseases.

- **Clinical assessment and data collection**

All patients were subjected to detailed history taking and full clinical examination (General examination, Cardiac examination, Chest examination, Abdominal, back examination and Neurological examination) in addition to laboratory investigations, EEG and overnight polysomnography. A sleep questionnaire (ISQ) was given to parents. Overnight polysomnographic recordings were scored for sleep architecture according to American Academy of Sleep Medicine criteria.

STATISTICAL ANALYSIS:

Data were analyzed using NCSS© 12 Statistical Software 2018 (*NCSS, LLC. Kaysville, Utah, USA*)

Continuous numerical data were presented as mean and standard deviation and between-group differences were compared using one-way analysis of variance (ANOVA) with application of the Tukey test for post hoc comparison if needed.

Categorical data were presented as number and percentage. Associations among ordinal variables were tested using Somer's d.

3. RESULTS:

Table (1): Age and age at onset in the study population

					Percentile		
Variable	Min.	Max.	Mean	SD	25^{th} p.	Median	75^{th} p.
Age (months)	9.0	48.0	25.4	9.8	18.0	24.0	30.0
Age at onset of spells (months)	6	31	13	6	9	12	16

Min. = minimum, Max. = maximum, SD = standard deviation, 25th p. = 25th percentile, 75th p. = 75th percentile.

The mean age of the studied patients at the time of the study was 25.4 ± 9.8 months old. The age of the youngest patient among the study group was 9 months old and the oldest patient was 48 months (4 years) old. The mean age at onset of BHS among our study group was 13 ± 6 months, (minimum 6 months and maximum 31 months old).

Table (2): Description of BHS

		n	%
Type of spells	Cyanotic	26	87%
	Pallid	4	13%
Frequency of spells	Mild	9	30%
	Moderate	13	43%
	Severe	8	27%
Severity of spells	Mild	9	30%
	Moderate	12	40%
	Severe	9	30%

Data are number (n) and percentage (%).

Patients in our study population are suffering from two types of breath holding spells, cyanotic spells and pallid spells. Twenty-six patients suffered from the cyanotic type representing 86.7% of the study group while four patients suffered from the pallid type representing 13.3%.

Nine patients representing 30% suffered from a mild form of the spells, twelve patients representing 40% suffered from a moderate form of the spells while nine patients representing 30% suffered from a severe form of the spells.

The mild group contributed 30% of patients, moderate group contributed 43.3% of patients and severe form contributed 26.7% of patients.

Table (3): Infant sleep questionnaire (ISQ)

					Percentile		
Variable	**Min.**	**Max.**	**Mean**	**SD**	**25th p.**	**Median**	**75th p.**
ISQ1 score	0.0	38.0	19.6	11.0	10.0	20.0	28.0
			n	%			
ISQ2	Normal sleep		13	43%			
	Sleep disorders n= 17 57%	Mild	5	17%			
		Moderate	8	27%			
		Severe	4	13%			
Sleep disorders by Research Criteria	No sleep disorder		17	57%			
	Sleep disorders		13	43%			

Data are number (n) and percentage (%). Min. = minimum, Max. = maximum, SD = standard deviation, 25th p. = 25th percentile, 75th p. = 75th percentile.

According to ISQ2 patients 43% of children (13 children) had normal sleeping pattern while 57% had sleep difficulties (17 children), divided into three groups, 17% had mild sleeping difficulties (5 patients), 27% had moderate sleeping difficulties (8 patients) and 13% had severe sleeping difficulties (4 patients).

As regarding assessment of sleep disorders using research criteria which is part 3 of the ISQ, 57% (17 patients) had normal sleep while 43% (13 patients) experienced sleeping difficulties.

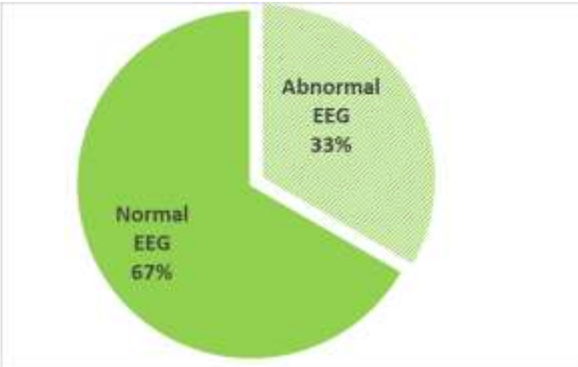

Figure (1): Prevalence of EEG abnormalities among study group

Table (4): Relation between the age at onset of spells and EEG findings, sleeping difficulties by ISQ2 or sleep disorders by Research criteria

			Age at onset of spells (months)			
Variable		**n**	**Mean**	**SD**	**F**	**p-value***
EEG	Abnormal	10	13	7	0.124	0.728
	Normal	20	14	6		
ISQ2	Normal sleep	13	16	8	5.199	**0.006**
	Mild difficulty	5	11#	3		
	Moderate difficulty	8	12	4		
	Severe difficulty	4	11	3		
Sleep disorder by Research Criteria	No sleep disorder	17	15	7	6.829	**0.014**
	Sleep disorder	13	11	4		

Data are number (n), mean and standard deviation (SD). F = F-statistic; *One-way analysis of variance (ANOVA); #p-value = 0.003 vs. Normal Sleep subgroup.

There were statistically significant relations between the age of patients at the onset of BHS and the sleeping difficulties determined by both ISQ2 and by Research criteria (p values = 0.006 and 0.014 respectively).

There was no statistically significant correlation between age of patients at onset of BHS and the EEG results.

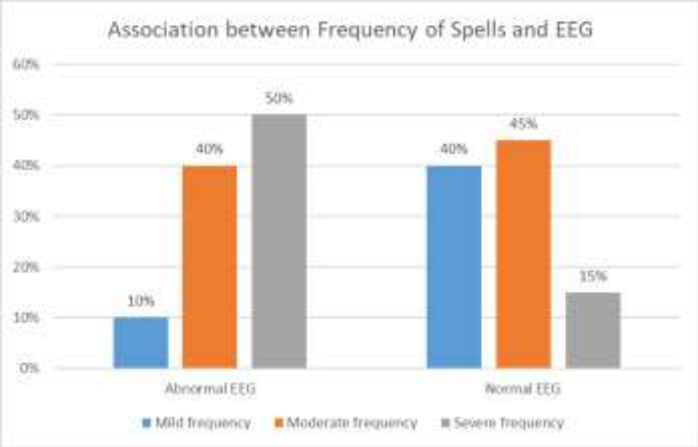

Figure (2): Association between the frequency of BHS and EEG abnormality.

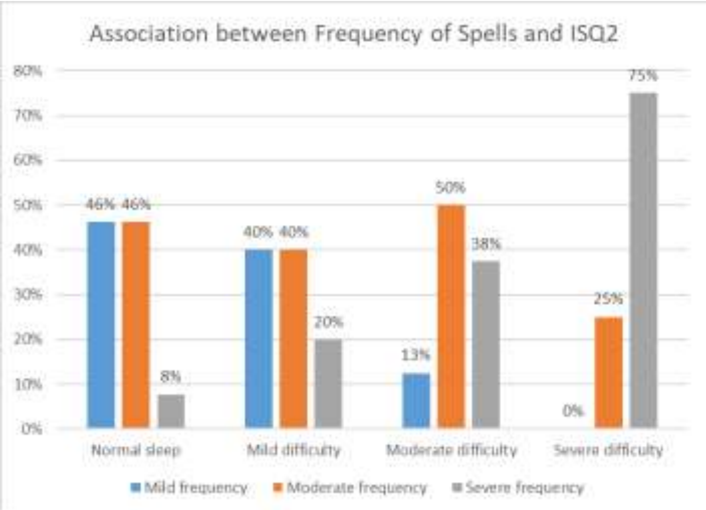

Figure (3): Association between the frequency of BHS and sleep difficulty as per the ISQ2.

Table (5): Correlation between age at onset, frequency and severity of spells and other numerical variables

Variable		Age at onset of spells	Frequency of spells	Severity of spells
Hemoglobin	Spearman's rho	0.188	-0.220	**-0.361***
	P-value	0.319	0.242	0.050
Hematocrit	Spearman's rho	0.285	-0.280	-0.209
	P-value	0.127	0.134	0.267
Serum iron	Spearman's rho	-0.034	0.104	-0.100
	P-value	0.859	0.585	0.601
Sleep efficiency	Spearman's rho	0.028	0.181	-0.311
	P-value	0.882	0.339	0.094
Apnea-hypopnea frequency	Spearman's rho	0.126	0.050	-0.145
	P-value	0.507	0.795	0.444
Obstructive apnea frequency	Spearman's rho	-	-	-
	P-value	-	-	-
Central apnea frequency	Spearman's rho	0.100	-0.054	-0.216
	P-value	0.600	0.775	0.252
Hypopnea frequency	Spearman's rho	0.160	0.235	-0.058
	P-value	0.398	0.211	0.761
N1 stage	Spearman's rho	0.264	-0.115	-0.155
	P-value	0.159	0.546	0.413
N2 stage	Spearman's rho	0.110	-0.044	0.114
	P-value	0.562	0.817	0.547

N3 stage	Spearman's rho	-0.196	0.110	-0.154
	P-value	0.298	0.564	0.416
REM stage	Spearman's rho	0.252	-0.253	-0.118
	P-value	0.180	0.177	0.534
Mean SpO_2	Spearman's rho	0.123	0.033	0.150
	P-value	0.517	0.863	0.429
Lowest SpO_2	Spearman's rho	-0.144	0.005	0.218
	P-value	0.447	0.978	0.248
LMI	Spearman's rho	-0.051	0.103	0.088
	P-value	0.789	0.590	0.644
PLM index	Spearman's rho	-0.260	-0.040	0.152
	P-value	0.165	0.835	0.421
Mean HR	Spearman's rho	-0.115	0.193	0.000
	P-value	0.546	0.306	1.000
ISQ1 score	Spearman's rho	**-0.393***	**0.452***	0.152
	P-value	**0.032**	**0.012**	0.423
ISQ2	Spearman's rho	-0.313	**0.513****	0.163
	P-value	0.092	**0.004**	0.389

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

There was a statistically significant inverse correlation between the age of patients at onset of BHS and sleeping difficulties in same patients determined by ISQ1 scores.
There was a statistically significant positive correlation between the frequency of BHS in our patients and their scores in ISQ1.
There was also a statistically significant positive correlation between frequency of BHS in our patients and their diagnosis of having sleeping difficulties determined by ISQ2.
There was a statistically significant inverse correlation between the severity of BHS in our patients and their hemoglobin levels.

4. DISCUSSION

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 ultimately loss of consciousness and postural tone. The diagnosis of BHS is made readily by history; however, other neurologic and cardiac etiologies for syncope should be excluded[7].
Our study was conducted on thirty children diagnosed with BHS, 18 males and 12 females, with mean age 25.4 ± 9.8 months (ranged 9-48 months old), recruited from the Neuropediatric Outpatient Clinic, Cairo University Children Hospital (CUCH) in the time period between January 2017 and December 2018. We had 26 patients (86.7%) had cyanotic BHS while 4 patients (13.3%) had pallid BHS.
Kahn et al.8 performed the first sleep investigation of children with BHS. Their study aimed to assess the airway obstructions during sleep in infants with BHS. They enrolled 71 infants with BHS with mean age of 17.3 ± 8.7 weeks (ranged 3 – 30 weeks) in the time period between January 1985 and March 1989. 45 % of the studied infants were males. They compared their study group to same number of healthy infants with matched age and gender as controls. The infants of both groups were studied during a one-night monitoring session of PSG, and the 142 sleep recordings were analyzed.
In our study spells exhibited varied degrees of severity, 30% of patients suffered from a mild form of the spells, 40% patients suffered from a moderate form of the spells while 30% patients suffered from a severe form (followed by loss of consciousness or seizure). While among Kahn et al.8 study group, 34 infants (48%) had mild to moderate BHS without loss of consciousness, and 37 (53%) had severe spells associated with loss of consciousness (21 with cyanotic BHS, 14 with pallid BHS, and 2 with mixed BHS).
Interestingly, our study showed a statistically significant relation between the age of patients at the onset of BHS and the sleeping difficulties determined by both infant sleep questionnaire 2 (ISQ2) and by Research criteria (p values of 0.006 and 0.014 respectively). Results showed that normal sleep according to ISQ (ISQ2 and Research criteria) was noticed in patients with older age at onset of BHS (mean age of 16 ± 8 months by ISQ2, mean age of 15 ± 7 months by Research Criteria), while sleeping difficulties with different levels were elicited in patients of younger age at the onset of BHS.
Results also showed a statistically significant inverse correlation between the age of patients at onset of BHS and scores of patients in the ISQ1 reflecting more sleeping difficulties (Spearman's rho -0.393* and p value 0.032) showing that patients with younger age at onset of BHS suffered from more sleeping difficulties reflected by higher scores in ISQ1.

Breath-holding infants have repeated airway obstructions during sleep in association with sleep fragmentation. This finding could contribute to a better understanding of the pathophysiology of breath-holding attacks, because these could reflect a complex immaturity of upper airway control. During sleep the airway obstructions of infants are generally innocuous, being short and not accompanied by significant bradycardia or oxygen desaturation. The general outlook for infants with breath-holding spells is excellent, but it remains to be established whether the fragmented sleep structure affects their psychomotor development or behavior[9].

In our study, according to the ISQ2, 56.7% of BHS patients had sleeping difficulties (16.7% had mild sleeping difficulties, 26.7% had moderate sleeping difficulties and 13.3% had severe sleeping difficulties) which matches **Kahn et al.**[8] as they noted that infants with such BHS had more disrupted nocturnal sleep, decreased stage 3 sleep, more frequent arousals, and increased sweating during sleep compared with controls.

In lights of this, our results showed statistically significant positive correlation between the frequency of BHS in our patients and their scores in ISQ1 denoting their sleeping difficulties (Spearman's rho 0.452* and p value 0.012) showing that patients with higher scores in ISQ1 implying more sleeping difficulties had experienced higher frequency of BHS.

Also, there were statistically significant positive associations between frequency of BHS and sleeping difficulties determined by both ISQ2 and sleep disorder by Research criteria (d = 0.438, p-value <0.001 & d = 0.624, p-value <0.001 respectively).

Continuing on this line, there was also a statistically significant positive correlation between frequency of BHS in our patients and their diagnosis with sleeping difficulties determined by ISQ2 and (Spearman's rho 0.513** and p value 0.004) showing that patients with sleeping difficulties according to ISQ2 had experienced higher frequency of BHS.

On the contrary, we found no relation between severity of BHS in our patients and their age, sleeping difficulties or EEG abnormalities. These results were consistent with those of **Kahn et al.**[8] who claimed no established relation between severity of spells and their patients' age or their sleep characteristics.

Furthermore, several studies have revealed that iron supplementation to children with breath-holding spells with concomitant anemia was effective in decreasing the frequency and severity of the spells. Iron deficiency anemia may affect oxygen uptake in the lungs causing tissue hypoxia, including the central nervous system. How iron deficiency leads to breath-holding spells remains unknown. However, it may be related to the fact that iron is important for catecholamine metabolism and functioning of various enzymes and neurotransmitters[10].

Orii et al.[11] documented the improvement of hematologic data and disappearance of attacks in all BHS patients suffering from mild iron deficiency anemia treated with iron during their study. In addition, they suggested that autonomic dysregulation in children with BHS can be improved by iron supplementation. ECG reading among their patients revealed low-frequency/high-frequency ratio decreased and the RR intervals > 50 milliseconds increased during sleep after iron treatment. It appears that supplementation of iron is effective in improving the variability in heart rate or sinus rhythm.

5. CONCLUSION

We concluded that children with BHS have showed a remarkable degree of sleeping difficulties and sleep fragmentation. This finding could contribute to a better understanding of the pathophysiology of breath-holding attacks. Patients with one or more risk factors as sleeping difficulties, sleep apneas, abnormal EEG or iron deficiency anemia will have the tendency to experience more frequent and more severe forms of BHS.

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