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Evaluation of the Predictors of Breath Holding Spell (BHS) in under 5-Year-Old Children in Iran: A Hospital-Based Case-Control Study

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Abstract

Background: Breath holding spell (BHS) is a sudden, reflexive, non-epileptic phenomenon that is common in infancy and early childhood. The aim of this study was to determine the predictors of breath holding spell (BHS) in children under 5 in Iran.

Methods: The study was a case-control study (case, n=55; control, n=55). The cases were selected from children with BHS who had been referred to Mohammad Kermanshahi Hospital of Kermanshah, during 2019. Then, for each case, one control was selected among the children who referred to other wards of this hospital for reasons other than BHS.The data collection tool was a data collection form including demographic, family, obstetric and biochemical characteristics. The biochemical parameters (such as serum calcium, magnesium, albumin, phosphorus and vitamin D levels) were measured by a fully automatic auto-analyzer (Prestige 24i Tokyo-Boeki, Japan). Univariate and multivariate logistic regression models were used to data analysis by STATA 14.

Results: The mean age of children for case and control groups were 22.85 ± 15.34 and 23.29 ± 16.91 months, respectively. The numbers of boys were 32(58.20) and 29(52.70) for case and control groups; respectively. The multivariate logistic regression model showed that the calcium (OR=9.03; 95% CI: 2.51 – 32.48), household size (OR=0.19; 95% CI: 0.04 – 0.90), paternal education (OR=0.48; 95% CI: 0.24 – 0.97), and history of mental illness in family (OR=8.97; 95% CI: 1.15 – 69.72) were, statistically, the most important predictors of BHS in children under 5 years.

Conclusion: Calcium, household size, paternal education and history of mental illness in family were the most important predictors of BHS in children under 5 years; however, studies with larger sample size are required.

Key Words: Breath Holding Spell (BHS), Case-control Study, Children under 5 Years, Predictor.

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1- INTRODUCTION

Breath holding spell (BHS) is a sudden, reflexive, non-epileptic phenomenon that is common in infancy and early childhood. Patients with these spells usually refer to neurology and pediatric heart clinics to check for heart disease or seizures (1, 2). The spells always occur during wake up following a mild trauma or nervous stress and last less than a minute. Symptoms appear in three forms cyanotic, pallid and mixed based on facial discoloration in children and characterized by a decrease in level of consciousness and tone. Finally, the spells are automatically terminated without any action (3-5). Prevalence of BHS is about 0.1- 4.6% in children 6 months to 5 years of age. It usually starts between 6-18 months of age and improves at the age of 4 - 5 years; however, the small numbers of cases have been reported at the age of 7 years (6-8). In terms of gender, the prevalence of BHS is almost the same in boys and girls, although it is slightly more common in boys. Additionally, children with BHS have a family history in 20-35% of cases (9-11).

Studies have shown that an autosomal mode of inheritance with reduced penetration may play a role in onset of sever spells (2, 12). Generally, the etiology of the BHS is not yet clear, however, most of the studies have suggested that the autonomic nervoussystem dysregulation may be involved in the pathogenesis of the disease. In addition, some studies have suggested the association of 16p11.2 microdeletion syndrome and Riley-Day syndrome with early-onset, recurrent, and severe BHS (13-15). It was previously thought that these spells would disappear with age and the development of the body's autonomic system; however, studies have shown that these children are more likely to fainting and sinus arrhythmia in future (16-18).

Various studies have investigated risk factors of BHS. A number of studies have suggested QT dispersion as an important risk factor, since the QT interval in patients with BHS increases significantly (1, 2, 19). QT dispersion is a useful method for non-invasive evaluation of ventricular myocardial repolarization using superficial EKG, which indicates the risk of serious ventricular arrhythmias and coronary heart disease (20, 21). Some other studies have suggested changes in biochemical factors such as sodium, potassium, calcium, magnesium and selenium as affective factors in the development of this disease (11, 22). However, there are controversies about the role of each of these factors in the incidence of the BHS. Therefore, according to the above explanations and considering the limited comprehensive studies in Iran and the world about the role of all these factors in the incidence of this disease, this hospital-based case control study was designed; it aims at determining the predictors of breath holding spell (BHS) in children under 5 years of age referred to Mohammad Kermanshahi Hospital in Kermanshah city, Iran.

2- MATERIALS AND METHODS

2-1. Study Design and Subjects

This hospital-based case-control study was designed to determine the predictors of breath holding spell (BHS) in children less than 5 years of age referred to Mohammad Kermanshahi Hospital of Kermanshah city, Iran. The cases were selected from children with breath holding spell (BHS) who had been referred to the mentioned Hospital during 2019, consecutively. Then, for each case, one control was selected among the children who had referred to other wards of the hospital for reasons other than breath holding spell (BHS). Inclusion criteria regarding the cases consisted of age<5 years, having breath holding spell (BHS), and informed consent to participate in the

research. Exclusion criteria in regard to the cases consisted of history of seizures, organic diseases or the diseases affecting the electrocardiogram (ECG or EKG), history of use of drugs affecting QT interval such as erythromycin, clarithromycin, and furosemide. Inclusion criteria for controls consisted of age<5 years, lack of breath holding spell (BHS), and informed consent to participate in the study and exclusion criteria for controls were the same as those mentioned for cases.

2-2. Data Collection

The data collection tool was a data collection form consisting of demographic information (such as age, sex, birth weight, etc.) family and demographic characteristics (such as employment, education and smoking status of parents), obstetric (such as type of delivery and milk consumption during infancy) and biochemical characteristics (such as serum calcium, magnesium, albumin, phosphorus and vitamin D levels). After obtaining the informed consent from the participants' parents, some of the information was obtained through medical records and interviews with the child's parents and some other (biochemical parameters) was gathered with direct measurement. To measure biochemical parameters of magnesium, calcium, phosphorus and vitamin D, 5 ml of intravenous blood was taken from all participants then centrifuged at 3500 rpm for 10 minutes and kept at -20 ° C. Finally, the levels of these parameters were measured by fully automatic autoanalyzer (Prestige 24i Tokyo-Boeki, Japan). It should be noted that the levels of all these parameters were measured in both study groups.

2-3. Statistical analysis

Data were analyzed using Stata software version 14.0 (Stata Corp, College Station, TX, USA). For descriptive analyses, the mean, standard deviation (SD), and number (%) were calculated. Then, univariate and multivariate logistic regression model was used to determine the predictors of breath holding spell (BHS) in children under 5 years, and crude and adjusted odds ratio (OR) with 95% confidence interval (CI) were estimated. P-value<0.05 was considered to indicate statistical significance.

3- RESULTS

This hospital-based case-control study was performed to determine the predictors of breath holding spell (BHS) in children under 5 years of age referred to Mohammad Kermanshahi Hospital of Kermanshah city (Iran) in 2019. A total of 55 cases with BHS and 55 controls were enrolled in the study. **Tables 1 and 2** show the demographic, obstetric and laboratory characteristics of children under study in the case and control groups.

As can be seen in **table 1**, the mean ages of children for case and control groups were 22.85 ± 15.34 and 23.29 ± 16.91 months, respectively. There was no significant difference in the age of the patients in the two groups (P-value>0.05). The numbers of boys were 32 (58.20) and 29 (52.70) for case and control groups; respectively. Also, the means of birth weight, calcium, magnesium, and phosphorus and QT interval for case and control groups were 3090 ± 370 vs. 3150 ± 340, 9.34 ± 0.64 vs. 9.94 ± 0.68, 2.23 ± 0.36 vs. 2.25 ± 0.32 , 4.81 ± 0.77 vs. 4.87 ± 1.01 , 0.41 ± 0.02 vs. 0.40 ± 0.01, respectively. In addition, children with family history of BSH and Iron deficiency anemia were 17 (30.90) vs. 4 (7.30) and 27 (49.10) vs. 16 (29.10) in case and control groups, respectively. Other details of these variables can be seen in **Table 2.**

Table-1: Quantitative characteristics of children under study in the case and control groups

Quantitative Variables	Groups	Number	Mean	S.D*
Age (month)	Case	55	22.85	15.34
	Control	55	23.29	16.91
Birth Weight (gr)	Case	55	3090	370
	Control	55	3150	340
Calcium (mg/dl)	Case	55	9.34	0.64
	Control	55	9.94	0.68
Magnesium (mg/dl)	Case	55	2.23	0.36
	Control	55	2.25	0.32
Phosphorus (mg/dl)	Case	55	4.81	0.77
	Control	55	4.87	1.01
QT interval	Case	55	0.41	0.02
	Control	55	0.40	0.01

*S.D: Standard Deviation

Table-2: Qualitative characteristics of children under study in the case and control groups

Qualitative Variables		Groups	
		Case (%)	Control (%)
Sex	Boy	32 (58.20)	29 (52.70)
	Girl	23 (41.80)	26 (47.30)
Type of delivery	Vaginal delivery	37 (67.30)	34 (61.80)
	Cesarean section	18 (32.70)	21 (38.20)
Birth order	1	17 (30.90)	21 (38.20)
	2	29 (52.70)	31 (56.30)
	≥3	9 (16.40)	3 (5.50)
Type of milk during infancy	Breast milk	29 (52.80)	33 (60.00)
	Powdered milk	13 (23.60)	12 (21.80)
	Both	13 (23.60)	10 (8.20)
Family history of BSH	Yes	17 (30.90)	4 (7.30)
	No	38 (69.10)	51 (92.30)
Iron deficiency anemia in child	Yes	27 (49.10)	16 (29.10)
	No	28 (50.90)	39 (70.90)
Vitamin D	<30	35 (63.60)	24 (43.60)
	>30	20 (36.40)	31 (56.40)

Table 3 shows family characteristics of the children under study in the case and control groups. In the case and control groups, respectively, 23.60 and 7.30% fathers were smokers; and addiction in family and history of mental illness in family were 20 vs. 10.90% and 29.10 vs. 9.10%; respectively. Other variables can be seen in **Table 3**.

Table 4 shows predictors of breath holding spell (BHS) for children under 5 years of age in the case and control groups by univariate logistic regression model. As can be seen, a statistically significant difference was found between the case and the control groups in term of the birth order, family history of BSH, Iron deficiency anemia in child, calcium,

vitamin D, QT interval, household size, paternal smoking , paternal education, addiction in family and history of mental illness in family (p ≤0.20).

Table-3: Family characteristics of the children under study in the case and control groups

Qualitative Variables		Groups	
		Case (%)	Control (%)
Household size	3	14 (25.50)	22 (40.00)
	4	29 (52.70)	28 (50.90)
	≥5	12 (21.80)	5 (9.10)
Maternal occupation	Housewife	37 (67.30)	40 (72.70)
	Employed	18 (32.70)	15 (27.30)
Status of supervision	Both parents	52 (94.50)	54 (98.20)
	Other	3 (5.50)	1 (1.80)
Paternal smoking	Yes	13 (23.60)	4 (7.30)
	No	42 (76.40)	51 (92.70)
Maternal smoking	Yes	1 (1.80)	0 (0.00)
	No	54 (98.20)	55 (100)
Paternal education	Non-academic	23 (41.80)	35 (63.60)
	Academic	32 (58.20)	20 (36.40)
Maternal education	Non-academic	30 (54.60)	37 (67.30)
	Academic	25 (45.40)	18 (32.70)
Addiction in family	Yes	11 (20.00)	6 (10.90)
	No	44 (80.00)	49 (89.10)
Mental illness in Family	Yes	16 (29.10)	5 (9.10)
	No	39 (70.90)	50 (90.90)
Place of residence	City	44 (80.00)	46 (83.60)
	Village	11 (20.00)	11 (16.40)

Then, in order to eliminate potential confounding variables, the variables with P≤0.20 in univariate logistic regression model were introduced to the multivariate logistic regression model; simultaneously. **Table 5** shows OR and 95% CI derived from multivariate logistic regression model for final predictors of breath holding spell (BHS) in children under 5 years of age. As can be seen, after adjusting for the confounding variables, the calcium (OR=9.03; 95% CI: 2.51 – 32.48), and household size (OR=0.19; 95% CI: 0.04 – 0.90), paternal education (OR=0.48; 95% CI: 0.24 – 0.97), and history of mental illness in family (OR=8.97; 95% CI: 1.15 – 69.72) were, statistically, the most important predictors of breath holding spell (BHS) among under 5-year children **(**P<0.05**)**. For example, adjusted OR for calcium was 9.03 (95% CI: 2.51 – 32.48). This means that along with the per one unit increase of calcium, the odds of holding breath spell (BHS) increases up to 9.02 times after adjusting for the confounding variables.

Table-4: Predictors of breath holding spell (BHS) in children under 5 years by univariate logistic regression model

Variables	Crude OR	95% Confidence Interval	P-value
Age (year)	1.002	0.98 – 1.02	0.886
Sex	1.24	0.59 – 2.65	0.565
Birth Weight (gr)	1.56	0.54 – 4.50	0.411
Type of delivery	1.27	0.58 – 2.77	0.550
Birth order	0.60	0.32 – 1.11	0.103
Type of milk during infancy	0.82	0.51 – 1.31	0.408
Family history of BSH	5.70	1.77 – 18.33	0.003
Iron deficiency anemia in child	2.35	1.07 – 5.01	0.033
Calcium (mg/dl)	4.04	2.005 – 8.14	<0.001
Magnesium (mg/dl)	1.14	0.38 – 3.38	0.814
Phosphorus (mg/dl)	1.08	0.71 – 1.64	0.722
Vitamin D	2.26	1.05 – 4.86	0.037
QT interval	6.57×10^{-20}	1.81×10^{-23}– 2.35×10^{-7}	0.003
Household size	0.53	0.30 – 0.93	0.027
Maternal occupation	0.77	0.34 – 1.74	0.533
Status of supervision	0.34	0.04 – 2.56	0.295
Paternal smoking	3.95	1.20 – 13.002	0.024
Paternal education	0.75	0.55 – 1.01	0.062
Maternal education	0.92	0.69 – 1.23	0.588
Addiction in family	2.04	0.70 – 5.98	0.193
History of Mental illness in Family	4.10	1.38 – 2.17	0.011
Place of residence	0.78	0.30 – 2.07	0.621

*P-Values ≤ 0.20 were considered significant to enter the Multivariable Logistic Regression Model

Table-5: Predictors of breath holding spell (BHS) in children under 5 years by multivariate logistic regression model

Variable	Adjusted OR	95% Confidence Interval	P-Value
Birth order	1.95	0.36 – 10.60	0.440
Family history of BSH	4.25	0.75 – 24.13	0.103
Iron deficiency anemia in child	1.19	0.31 – 4.56	0.790
Calcium (mg/dl)	9.03	2.51 – 32.48	0.001
Vitamin D	1.12	0.23 – 5.61	0.885
QT interval	3.08×10^{-7}	7.04×10^{-28}– 1.35×10^{14}	0.536
Household size	0.19	0.04 – 0.90	0.037
Paternal smoking	2.61	0.87 – 7.56	0.675
Paternal education	0.48	0.24 – 0.97	0.041
Addiction in family	1.16	0.95 – 5.57	0.870
History of mental illness in family	8.97	1.15 – 69.72	0.036

4- DISCUSSION

This hospital-based case-control study was designed to determine the predictors of breath holding spell (BHS) in children under 5 years of age referred to Mohammad Kermanshahi Hospital of Kermanshah city (Iran) in 2019. The results of univariate logistic regression model showed a statistically significant difference between the case and the control groups in terms of the birth order, family history of BSH, Iron deficiency anemia in child, calcium, vitamin D, QT interval, household size, paternal smoking, paternal education, addiction in family and history of mental illness in family ($P \leq 0.20$). However, the multivariate logistic regression model showed that the calcium (OR=9.03; 95% CI: 2.51 – 32.48), household size (OR=0.19; 95% CI: 0.04 – 0.90), paternal education (OR=0.48; 95% CI: 0.24–0.97), and history of mental illness in family (OR=8.97; 95% CI: 1.15–69.72) were the most important predictors of BHS in children under 5 years.

To the best of our knowledge, this research is one of the first studies that have examined the different predictors of BHS in children under 5 years of age. In our study, the positive family history of BSH in cases was higher than in the controls (30.90 vs. 7.30). However, this difference was not statistically significant in multivariate model; and this was inconsistent with results of the similar studies in this regard (2, 15, 23, 24). This inconsistency can be due to two reasons: first, in most studies that have examined the risk factors for BSH, comparisons between cases and controls have been made in a univariate model; perhaps they would have reached the same conclusion, if they had controlled the effect of other important confounding variables in the multivariate model. Second, it may be due to the relatively small sample size and use of the hospital controls, because the hospital controls are different from general population and usually the level of risk factors in them are higher than in the general population; and this can affect the results (25). Therefore, studies with higher sample size and the use of population controls (population-based case-control studies) are recommended.

In the present study, the mean QT interval in the cases was higher than that of the controls (0.41 ± 0.02 vs. 0.40 ± 0.01). However, this factor was not recognized as an important predictor in the multivariate model, and this was in contrast with results of the some studies in this area (1, 2, 19). These studies suggests that the QTc interval is significantly longer in patients with BHS than in normal children. This is a sign of cardiac repolarization disorder as well as an increased risk of cardiac arrhythmia in BHS patients (26). Also, Anil et al., suggested that the increase in QT dispersion in patients with BHS may be due to the presence of more serious autonomic dysfunctions in them in comparison to the control group (27). Of course, there were some other studies that were in line with our results and did not find a difference between QT and QTc intervals in patients with BHS and healthy children (15). The reasons for these discrepancies could be differences in the method of data analysis (univariate vs. multivariate), the use of hospital or healthy controls, and the sample size. However, the careful examination of the ECG, Long QT syndrome (LQTS), rhythm abnormalities and autonomic dysfunction in patients with BHS is recommended (19).

Furthermore, this study demonstrated a statistically significant relationship between calcium and the incidence of the BHS in this study (OR=9.03; 95% CI: 2.51 – 32.48). This was in line with other similar studies. A study by Özkale et al., aimed to assess the associations between BHS and serum magnesium and calcium levels showed that hemoglobin, calcium

and phosphorus levels in both case and control groups were in the normal range, however, their mean in the case group was significantly lower than the control group. In addition, there was no statistically significant difference between the two groups under study in terms of mean serum Mg level or Calcium / Magnesium (Ca / Mg) ratio. Ultimately, the researchers concluded that low levels of hemoglobin, calcium and phosphorus may reduce the threshold BHS and be risk factors for the development of BHS (22). Besides, studies have shown cerebral hypoperfusion, seizures and loss of consciousness can be consequences of autonomic dysregulation and heart rate variability (HRV), which controls heart function; and can be an important indicator of autonomic dysregulation (19, 27, 28). Furthermore, serum electrolyte levels including sodium (Na), potassium (K), calcium (Ca), and magnesium (Mg) can directly affect heart muscle excitability and heart rate, and ultimately affect blood pressure (29, 30). In addition, researchers have suggested that Ca and Mg levels are involved in the development of cardiovascular disease, especially sudden cardiac death (31, 32). Devisetty et al., have revealed that dysfunction of the autonomic nervous system may be due to decreased serum calcium levels in patients with BHS. The effect of Ca on HRV may be due to the role of Ca on cardiac muscle excitability and blood pressure. Ca supplementation can affect blood pressure, especially systolic blood pressure, and ultimately affects HRV(33). Therefore, this study and other similar studies suggest that the low levels of serum Ca and other electrolytes may be risk factors for BHS, however, more detailed studies with larger sample sizes to confirm these findings is recommended.

4-1. Strengths and Limitations

Perhaps the most important strength of this study is the design (case- control study), and having a control group. The second strength of the present study is hospital controls for two reasons: first, we are faced with differential misclassification in case-control studies, in other words, the parents of the case group, due to their awareness of their child's illness, think about the possible causes, more than the parents of the control group. Therefore, the recall bias does not occur in the same way in the case and control groups; and, ultimately, leads to differential misclassification and confounds the results. Using hospital controls is one of the most common methods to control the recall bias and differential misclassification. Second, given that we usually could not determine the characteristics of the reference population from which the cases are selected, comparison of cases and controls referred to the same hospital seems more logical; because, these participants must have come from the same case community. In this way, the selection bias of hospital cases is compensated by selecting a control group from a similar reference population. And, the most important disadvantage of this study may be the relatively small sample size, so if possible, studies with a higher sample size are recommended.

5- CONCLUSION

The results of the present study show Calcium, household size, paternal education and history of mental illness in family were, statistically, the most important predictors of BHS in children under 5 years of age; however, studies with larger sample sizes are required. The results also show that increased iron deficiency anemia, increased QT interval, decreased serum calcium and vitamin D levels are associated with breath holding spell (BHS) in less than 5 years old children.

6- ETHICS APPROVAL

Before data collection, the aims of the research were explained to the child's parents; then informed consent was obtained from them. In addition, this study was performed according to the principles expressed in the Declaration of Helsinki and was approved by the Deputy of Research and Ethics Committee of Kermanshah University of Medical Sciences (Iran) (IR.KUMS.REC.1398.748).

7- CONFLICT OF INTEREST: None.

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