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Can the Proinflammatory process affect breath-holding spells?

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Abstract

Breath-holding occurs after often pain, anger, crying, trauma, etc. in early childhood. It is defined as episodes of breathlessness and discoloration. Although the pathophysiology of breath-holding is not fully known, it is thought to be due to many factors. Factors such as genetic predisposition, iron deficiency anemia, autonomic nervous system immaturity, vagal-mediated cardiac inhibition, delayed myelination of the brain stem have been blamed in the etiopathogenesis. In our study, we aimed to evaluate the role of lymphocyte/monocyte ratio, neutrophil/lymphocyte ratio, neutrophil/monocyte ratio, MPV/platelet ratio parameters, which are indirect markers of inflammation, in etiopathogenesis. The files of 48 patients who were diagnosed with breath-holding in the pediatric neurology clinic of Balıkesir University Faculty of Medicine between 01.01.2020-01.01.2021 were retrospectively reviewed. The demographic characteristics and laboratory results of 42 healthy children who were admitted to the pediatric clinic in the same period and who were similar to the study group were compared. When the breath-holding was compared with the control group; age, WBC, hemoglobin, hematocrit, MCV, serum iron, serum iron-binding capacity, ferritin, lymphocyte, lymphocyte percentage, neutrophil percentage, neutrophil/lymphocyte ratio was found to be significantly different. Neutrophil percentage, lymphocyte percentage, lymphocyte, neutrophil/lymphocyte ratio which was found to be significantly different are accepted as indicators of subclinical infection or systemic inflammatory response. It is necessary to investigate whether infection, which is one of the most common causes of inflammation in children, is a triggering factor in breath-holding. We think that the presence of infection and/or inflammation should be excluded in the etiopathogenesis of breath-holding. We believe that it would be appropriate to evaluate the lymphocyte/monocyte ratio, neutrophil/lymphocyte ratio, neutrophil/monocyte ratio, MPV / platelet ratio, which is accepted as proinflammation parameters of patients with breath-holding.

Keywords: Breath-holding, proinflammation, inflammatory parameters

Introduction

Breath-holding spells are defined as attacks involving cessation of breathing and color change, frequently triggered by crying and generally occurring after pain, anger, etc., in early childhood. They are classified as cyanotic, pallid, or mixed, depending on the color change. Loss of consciousness may occur during attacks. Breath-holding spells can be observed in approximately 1-4.6% of healthy children [1]. Positive family history has been shown to increase the risk of attack 13.11-fold [2]. Breath-holding spells generally commence between six and 13 months of age and can conclude spontaneously at 36 months. They may rarely persist until six years of age. The attack frequency can vary from once every 3-4 monthsto several times a day [3]. The frequency of attacks has been observed to decrease or cease entirely with age [4]. Breath-holding spells last between two and 20 seconds, and muscle contraction may develop if the duration exceeds 10 seconds. Brief relaxation may occur following contraction. Spells are classified as cyanotic, pallid, or mixed, depending on the color change at the time of attack [5]. Patients generally return to normal levels of consciousness and regular respiration shortly after breath-holding spells and continue with their normal activities from where they were interrupted.

A potential disposition to breath-holding spells or prolongation of attacks has been determined in patients with iron deficiency [6]. Iron plays an important role in the regulation of neurological functions. It is also involved in the activity of several enzymes, including monoamine oxidase, in the central nervous system [7]. Although iron deficiency has been implicated in etiopathogenesis, numerous epidemiological, pathophysiological, and clinical studies have been performed to investigate the etiology of breath-holding spells. However, the number of studies involving tests showing inflammation in patients experiencing breath-holding spells is limited. There is therefore a need for studies investigating the presence of inflammation in etiopathogenesis. The purpose of this study was to evaluate the place in the etiopathogenesis of the lymphocyte/monocyte ratio, neutrophil/lymphocyte ratio, neutrophil/monocyte ratio, mean platelet volume (MPV)/ platelet ratio, indirect inflammatory markers, in pediatric patients diagnosed with breath-holding spells and followed-up in our clinic.

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Materials and Methods

The files of 48 patients aged between six months and six years presenting to the Balıkesir University Medical Faculty Pediatric Neurology Clinic, Turkey, between 01 January 2020, and 01, January 2021, and diagnosed with breath-holding spells were examined retrospectively. Forty-two comparable healthy children were included as the control group. Patients with a history of febrile seizures, epilepsy, or cardiac disease were excluded. Patients' age, sex, type of attack, attack-triggering factor, duration of the attack, number of attacks per month, white blood cell (WBC), hemoglobin (Hg), hematocrit (Hct), platelet, MPV, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration, mean corpuscular volume (MCV), plateletcrit (PCT), serum iron (Fe), serum iron-binding capacity (IBC), serum ferritin, vitamin D, vitamin B12, neutrophil, lymphocyte, monocyte, eosinophil, basophil, neutrophil percentage, lymphocyte percentage, monocyte percentage, eosinophil percentage, lymphocyte/monocyte ratio, neutrophil/lymphocyte ratio, neutrophil/monocyte ratio, and MPV/platelet ratio values were recorded. Approval for the study was granted by the Balıkesir University Medical Faculty ethical committee (no. 2021/162).

Statistical analysis

Data analysis was performed on SPSS version 23.0 software (SPSS Corp., Chicago, IL, USA). Normality was evaluated by Kolmogorov-Smirnov test. Descriptive statistics were expressed as the frequency and percentage for categorical variables, whereas quantitative data were expressed as the mean or median. Differences between normally distributed data were compared using Student's t-test. The Mann-Whitney U test was applied to compare non-normally distributed variables. p values ≤0.05 were regarded as significant.

Results

The 90 members of the study population consisted of 48 (53.3%) patients diagnosed with breath-holding spells and a 42-member (42.7%) control group. Forty-eight were girls [patient group 23 (25.5%), control group 25 (27.8%)] and 42 were boys [patient group 25 (27.8%), control group 17 (18.9%)]. The mean age of the study group was 40.4±19.6 months - 33.42±20.34 in the patient group and 56.09±10.3 in the control group. Patients with cyanotic type breath-holding spells were more numerous (87.5%) than those with acyanotic type spells (12.5%). The mean number of attacks per month was 2.3±2.2 (1. 1-10). The mean duration of attacks was 3±1.9 min. The most frequent attack-triggering factor was crying (58.3%, n:28). Other factors triggering attacks included trauma (14.6%, n:7), fear (12.5%, n:6), and anger (14.6%, n:7). (Table 1). Significant differences were determined between the group experiencing breath-holding spells and the control group in terms of age, and WBC, Hg, Hct, MCH, MCV, PCT, serum iron, serum IBC, ferritin, vitamin B12, lymphocyte, lymphocyte percentage, neutrophil percentage, and the neutrophil/lymphocyte ratio ($p<0.05$) (Table 2). No difference was observed between the two groups in terms of the other parameters.

Table 1. Demographic characteristics of the patients experiencing breath-holding spells

1	Sex; n (%)	**Female:** 48 (53.3%) **Patient group:** 23 (25.5%) **control group:** 25 (27.8%) **Male:** 42 (42.7%) **Patient group 25:** (27.8%) **control group 17:** (18.9%)
2	Age (months), (n=90)	40.4±19.6
3	Type of breath-holding spell; n (%)	**Cyanotic:** 42 (87.5%) **Acyanotic:** 6 (12.5%)
4	Number of attacks (monthly)	2.3±2.2 (1.1-10)
5	Duration of attacks (min)	3±1.9
6	Triggering factor; n (%)	**Trauma:** 7 (14.6%) **Crying:** 28 (58.3%) **Fear:** 6 (12.5%) **Anger:** 7 (14.6%)

(Mean ± SD, %, median, min-max)

Table2. Comparison of the parameters between the breath-holding spell patient and control groups

	Breath-holdingspellgroupMean±SD.median(min-max)	ControlgroupMean±SD.median(min-max)	p
Age(months)	33.42±20.34	56.09±10.3	0.01
WBC(×10³/mm³)	10.2±3.06	7.7±1.95	0.01
Hg(mg/dL)	11.6±1.02	12.43±0.86	0.01
Hct%	34.72±2.7	37.07±2.53	0.01
Plt(fl)	403.6±92.94	366.7±96.05	0.05
MPV(fl)	7.67±0.9	7.37±0.78	0.43
MPV/Plt	0.02±0.01	0.02±0.01	0.24
MCH(pg)	25.02±2.5	26.72±1.53	0.03
MCHC(mg/dL)	33.25±1.1	33.52±0.78	0.60
MCV(fL)	75.07±6.03	80.13±3.13	0.01
PCT	0.3±0.06	0.27±0.06	0.04
Fe(mg/dl)	29.54±14.53	76.04±25.93	0.00
Ironbindingcapacity(ug/dL)	441.62±98.47	352.92±39.46	0.00
Ferritin(ml/ng)	15.5±11.5	24±18	0.00
25OHD3(ng/mL)	32±10	27±12	0.20
VitaminB12(pg/ml)	282±310(220.100-1515)	385±147	0.00
Neutrophil(×10³/mm³)	3.02±1.43	2.96±1.07	0.59
Neutrophil%	31.30±13.32	38.42±9.38	0.04
Lymphocyte(×10³/mm³)	6.03±2.8	3.77±1.17	0.01
Lymphocyte%	57.83±13.50	49.63±10.23	0.02
Monocyte(×10³/mm³)	0.77±0.27	0.61±0.20	0.07
Monocyte%	7.6±1.8	8.9±7.8	0.76
Basophil(×10³/mm³)	0.32±0.45(0.1.0-8)	0.4±0.5(0.0-0.2)	0.14
Basophil%	0.8±0.86[0.5.(0.1-3.7)]	0.62±0.41	0.67
Eosinophil(×10³/mm³)	0.45±0.85[0.20.(0-3.9)]	0.31±0.32[0.20.(0-1.7)]	1.00
Eosinophil%	2.45±1.4	3.8±3.3	0.14
Neutrophil/lymphocyteratio	0.66±0.14	0.86±0.45	0.02
Neutrophil/monocyteratio	4.23±2.21	4.96±1.36	0.49
Lymphocyte/monocyteratio	8.17±2.82	6.69±2.39	0.07

Discussion

Breath-holding spells are a non-epileptic paroxysmal event seen at a rate of approximately 4.6% in early childhood and triggered by emotional and/or physical stimuli [7]. Positive family history and genetic disposition have been shown in the majority of studies [8]. Although these spells are reported to be more common in boys, no significant gender difference was found in the present research (Table 1). Children aged between six and 72 months were enrolled in this study, and a significant age difference was found between the breath-holding spell group (mean age 33.42±20.34 months) and the control group (mean age 56.09±10.3 months) ($p<0.01$). Although an age range of six to 72 months has been included in many studies, the majority of cases have been aged from six to 36 months. Breath-holding spells are most common in the first 12-24 months [9]. Cyanotic type breath-holding spells have been detected more frequently than the pallid type [5-10]. Cyanotic type spells were also more frequent in the present study (87.5%). Consistent with the previous literature, crying was the most common triggering factor (58.3%) (Table 1).

Significant differences were observed between the breath-holding spell group and the control group in terms of WBC ($p<0.01$), neutrophil percentage ($p<0.04$), lymphocyte ($p<0.01$), lymphocyte percentage ($p<0.02$), and neutrophil/lymphocyte ratio ($p<0.02$) values. These parameters are significant in showing subclinical infection or systemic inflammatory response. Inflammation is the body's self-defense mechanism and an innate immune mechanism. Several cells are involved in the immune system, such as the proinflammatory cells monocytes, macrophages, neutrophils, basophils, eosinophils, dendritic cells, and mast cells. The leukocyte (WBC) formula consists of neutrophil, monocyte, basophil, and eosinophil cells. Neutrophil, lymphocyte, and neutrophil/lymphocyte ratio values are regarded as markers of systemic inflammation [11].

The neutrophil/lymphocyte ratio is calculated by dividing the absolute neutrophil from a complete blood count in peripheral blood by the absolute lymphocyte count [12]. In a study of patients with febrile seizures, Göksugur et al. described the neutrophil/lymphocyte ratio as an important marker in terms of inflammation [13]. Liu et al. regarded the neutrophil/lymphocyte ratio, MPV, and red cell distribution width as three novel inflammatory markers. The use of the neutrophil/lymphocyte ratio as a systemic inflammatory response marker has been reported in several studies [11]. Liu et al. reported significant significances between their patient and control groups in terms of MPV, platelet, MPV/ platelet ratio, neutrophil (%), neutrophil count, lymphocyte (%), lymphocyte count, and neutrophil/lymphocyte ratio values [11]. The inflammatory marker neutrophil/lymphocyte ratio also differed significantly between the groups in the present study ($p<0.02$).

MPV represents the mean platelet volume and shows the size and production rate of platelets in the bone marrow. It is also used as a marker of platelet activation and inflammation [11-14]. Platelets contribute to systemic inflammation by producing the pro-inflammatory cytokine IL-1β [15]. Proinflammatory cytokines (IL-1α, IL-1β, and TGF-β1) stored inactivated platelet granules can be released during inflammation or tissue damage [11]. Platelet values differed significantly between the groups in the present study ($p<0.05$). The MPV/ platelet ratio can be employed as an inflammatory marker. No significant difference in terms of the MPV/platelet ratio was observed between the groups in this study ($p<0.24$).

PCT is a ratio showing the percentage of platelets to other cells in the blood. To put it another way, the volume represented by platelets can be expressed as the ratio to total blood volume [16]. When evaluated together with other complete blood parameters it provides information about platelet functions. B-lymphocytes, T-lymphocytes, monocytes, neutrophils, and dendritic cells play a role in the immune system by interacting with platelets [17]. PCT, a marker of platelet functions, differed significantly between the groups in the present study and maybe another inflammatory marker ($p<0.04$).

Although the pathophysiology of breath-holding spells is not fully understood, they are thought to be associated with several factors. A presence of a childhood history of breath-holding spells in the parents of children with breath-holding spells suggests that there may be an underlying genetic background [18]. In addition to a genetic etiology, autonomous nervous system immaturity, vagal-mediated cardiac inhibition, delayed brain stem myelination, and iron deficiency anemia have also been reported in the literature [19]. In cyanotic breath-holding spells, cerebral blood flow and the return of blood to the heart decrease in association with pulmonary shunt following prolonged crying, causing a transient loss of consciousness. However, in pallid breath-holding spells, transient loss of consciousness may occur with bradycardia or asystole following brief crying. Hyperstimulation in the sympathetic system is thought to be responsible in the cyanotic type, while vagal stimulation mechanisms are implicated in the pallid type [19]. DiMario et al. investigated autonomous nervous system irregularity in patients undergoing cyanotic type breath-holding spells [20].

Maayan et al. listed the presumed pathophysiological mechanisms involved in breath-holding spells as follows; (a) hypersensitivity of the parasympathetic system, (b) stimulation of the Hering-Breuer reflex preventing pulmonary expansion during inspiration and supporting expiration, (c) an altered central ventilatory response to hypoxia and hypercapnia, and (e) abnormal cerebrovascular and peripheral vascular autoregulation [21].

Vurucu et al. showed that delayed brain stem myelination may play a role in the etiology of breath-holding spells [22].

Iron deficiency anemia is regarded as a risk factor for breath-holding spells. A low hemoglobin level causes a decrease in the oxygen-carrying capacity of the blood and thus in the oxygenation of the brain, creating the risk of cyanotic breath-holding spells. Although the frequency of these attacks has been shown to decrease with iron therapy, the mechanism is not fully understood. However, certain mechanisms have been proposed, including (a) irritability and excessive crying being associated with iron deficiency, (b) iron playing a role as a cofactor in catecholamine metabolism and autonomic irregularity occurring following impaired catecholamine release in iron deficiency, and (c) interaction between cerebral erythropoietin, nitric oxide, and interleukin-1 being implicated in iron deficiency anemia [23]. Several studies investigating the pathophysiology of breath-holding spells have shown the importance of treating iron deficiency in reducing the

frequency of and preventing spells. Consistent with these studies, significant differences were determined in this study between patients experiencing breath-holding spells and the control group in terms of Hg ($p<0.01$), Hct ($p<0.01$), MCH ($p<0.03$), serum iron ($p<0.00$), and serum IBC ($p<0.00$). A significant difference was also observed in vitamin B12 ($p<0.00$). Patients were started on iron prepared at 6 mg/kg/day for the treatment of iron deficiency. Patients with vitamin B12 deficiency were also started on treatment and followed up.

Adult studies have investigated the parameters of MPV, platelet distribution width, and PCT. In their review study, Pogorzelska et al. determined high platelet index (PI) values in patients with diseases involving inflammation, such as type 2 diabetes, myocardial infarction, cancer, or conditions requiring surgery (appendicitis, mesenteric artery ischemia, cholecystitis, etc.). The authors suggested that PI values are of prognostic and predictive value in inflammation [24]. Efe et al. observed that PI values were correlated with the severity of disease in patients followed up in intensive care [16].

Although several factors have been considered in the investigation into the etiopathogenesis of breath-holding spells, there is a need for studies regarding the inflammatory process as a potential triggering factor. Inflammatory markers should be included during the evaluation of blood tests of patients with breath-holding spells during attacks. More extensive studies are now needed regarding whether inflammation affects the frequency, duration, and type of attack.

Conclusion

In conclusion, research is needed into whether the presence of viral or bacterial infection, one of the frequent causes of inflammation, is a triggering factor in breath-holding spells. We think that the presence of infection and/or inflammation should be excluded in the etiopathogenesis. Further studies are now needed to investigate whether inflammation plays a role in the etiopathogenesis of breath-holding spells. In the light of the studies described above and the present research, we think that the inflammatory parameters lymphocyte/monocyte ratio, neutrophil/lymphocyte ratio, neutrophil/monocyte ratio, and MPV/platelet ratio should also be considered when evaluating the tests of patients undergoing breath-holding spells.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical approval
Balıkesir University Faculty of Medicine Clinical Research Ethical Committee-2021/162.

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