

## Vitamin D Levels in Children Presenting with Breath-Holding Spells: An Example of A University Hospital\*

Katılma Nöbeti ile Başvuran Çocuklarda Vitamin D Düzeyleri: Bir Üniversite Hastanesi Örneği

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### ABSTRACT

**Aim:** This study aimed to examine the vitamin D levels in children who experience breath-holding spells (BHS) and to compare these levels with those of a healthy control group. The goal was to establish a connection between BHS and vitamin D levels.

**Method:** The records of 98 patients, who presented to the Pediatric Neurology and Pediatric Cardiology polyclinics of Adıyaman University Training and Research Hospital between December 2019 and October 2022, were retrospectively reviewed. Fifty-two patients who did not meet the inclusion criteria were excluded. The study included forty-six patients with BHS whose laboratory results were assessed and a healthy control group of fifty-three individuals. Fe, serum iron binding capacity, ferritin, vitamin B12, and vitamin D levels were measured in all patients.

**Results:** The study group comprised 46 patients (female/male ratio = 1.4), consisting of 27 girls (58.6%) and 19 boys (41.3%). Within our patient cohort, 39 individuals (84.8%) were diagnosed with cyanotic-type spells, three (6.5%) with pallid-type spells, and four (8.7%) with mixed-type spells. For patients experiencing BHS, a comprehensive analysis was conducted on parameters including complete blood count, iron levels, iron-binding capacity, ferritin levels, vitamin B12, and vitamin D levels. Although no significant correlation was identified with vitamin D levels in this study, noteworthy connections were established with lower hemoglobin levels, decreased vitamin B12 levels, and reduced ferritin levels. Moreover, upon exclusion of patients exhibiting low vitamin B12 values from the analysis, a statistically significant relationship emerged between iron deficiency anemia and the occurrence of BHS ( $p<0.05$ ).

**Conclusion:** The study results suggest no significant correlation between low vitamin D levels and BHS, which generally have a favorable prognosis. However, considering the potential connections between iron deficiency anemia and vitamin B2 levels, it is advisable to assess these factors routinely.

**Keywords:** Breath-holding spells, Child, Vitamin D

### ÖZET

**Amaç:** Bu çalışmanın amacı, katılma nöbetleri ile başvuran çocuklarda vitamin D düzeylerini araştırmak, bunları sağlıklı kontrol grubu ile karşılaştırmak ve nefes tutma nöbetleri ile vitamin D düzeyleri arasındaki ilişkiyi ortaya koymaktır.

**Yöntem:** Aralık 2019 ile Ekim 2022 tarihleri arasında Adıyaman Üniversitesi Eğitim ve Araştırma Hastanesi Çocuk Nöroloji ve Çocuk Kardiyoloji polikliniklerine başvuran 98 hastanın dosyaları retrospektif olarak incelendi. Dahil etme kriterlerini karşılamayan 52 hasta çalışma dışı bırakıldı. Kırk altı çocuk katılma nöbeti grubu, 53 sağlıklı çocuk kontrol grubu olarak çalışmaya dahil edilmiştir. Tüm hastalarda Fe, serum demir bağlama kapasitesi, ferritin, vitamin B12 ve vitamin D düzeyleri ölçüldü.

**Bulgular:** Çalışma grubu 27 kız (%58,6), 19 erkek (%41,3) olmak üzere 46 hastadan (K/E=1,4) oluşuyordu. Hasta grubumuzun 39'u (%84,8) siyanotik tip, 3'ü (%6,5) soluk tip ve 4'ü (%8,7) karışık tip katılma nöbeti tanısı almıştı. Katılma nöbetiyle başvuran hastaların özellikle tam kan sayımı, demir seviyeleri, demir bağlama kapasitesi, ferritin seviyeleri, vitamin B12 ve vitamin D seviyeleri gibi parametreler üzerinden kapsamlı bir analiz yapıldı. Bu çalışmada vitamin D seviyeleri ile anlamlı bir ilişki tespit edilmemiş olsa da düşük hemoglobin seviyeleri, azalmış B12 vitamini seviyeleri ve azalmış ferritin seviyeleri ile kayda değer bağlantılar kuruldu. Ayrıca B12 vitamini değerleri düşük olan hastaların analiz dışı bırakılmasıyla demir eksikliği anemisi ile katılma nöbetleri arasında istatistiksel olarak anlamlı bir ilişki ortaya çıktı ( $p<0,05$ ).

**Sonuç:** Çalışma sonuçları, düşük D vitamini düzeyleri ile genellikle olumlu prognoza sahip olan BHS arasında anlamlı bir ilişki olmadığını göstermektedir. Bununla birlikte, demir eksikliği anemisi ve vitamin B12 seviyeleri arasındaki potansiyel bağlantılar göz önünde bulundurulduğunda, bu faktörlerin rutin olarak değerlendirilmesi tavsiye edilmektedir.

**Anahtar kelimeler:** Katılma nöbeti, Çocuk, Vitamin D

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## Introduction

BHS represent a recurring non-epileptic phenomenon commonly observed during childhood, often triggering anxiety and panic among parents. It is common for families to misinterpret these episodes as seizures or cardiac arrests, leading to heightened anxiety levels. The characteristic feature of this condition is the occurrence of prolonged breath-holding following an exhalation. These spells can manifest in different forms, including pallid, cyanotic, or mixed types, which are determined by factors such as the loss of postural control, changes in skin color, and alterations in consciousness arising from irritation or discomfort.<sup>1</sup> Emotional stress often precipitates cyanotic BHS, whereas pallid spells manifest in response to sudden pain. Prolonged episodes may occasionally lead to myoclonic jerks and brief tonic seizures, often associated with cerebral hypoperfusion. Despite the mechanism remaining elusive, these manifestations may stem from a dysfunction within the autonomic nervous system. Furthermore, studies have indicated a potential correlation with iron deficiency anemia.<sup>2,3</sup> Many patients encounter their initial episode before reaching 18 months of age, although instances have also been observed in neonates<sup>4</sup>. A comprehensive medical history and meticulous observation of the patient's spells are essential for obtaining precise insights into BHS. Patients should be directed toward cardiological and neurological assessments when suspicions arise for further evaluation.

Vitamin D has been suggested to impact erythropoiesis potentially. Research indicates a potential association between vitamin D deficiency and increased susceptibility to anemia, reduced mean hemoglobin levels, and an elevated usage of erythrocyte-stimulating agents<sup>5</sup>. This study aims to investigate the impact of vitamin D deficiency, a topic that has received limited attention in the literature, on seizure occurrences and BHS.

## Materials and Methods

### Study Population

The Adiyaman University Training and Research Hospital is the only reference hospital in the city and provides health services at the 3<sup>rd</sup> level. There is an Assistant Professor in the Department of Pediatric Cardiology and a Pediatric Neurologist in the Department of Pediatric Neurology at the university hospital. Each year, 5500 patients apply to the hospital's pediatric cardiology department and 4500 patients apply to the pediatric neurology department. Between December 2019 and October 2022, 98 patients applied to the Pediatric Neurology and Pediatric Cardiology polyclinics of Adiyaman University Training and Research Hospital with the complaint of attending seizures.

### Patients

Patients who presented to the Pediatric Neurology and Pediatric Cardiology Polyclinics Adiyaman University Training and Research Hospital from December 2019 to October 2022 and were diagnosed with seizure episodes were identified and enrolled in the study. The inclusion criteria encompassed a diagnosis of generalized seizures, the absence of any other chronic condition potentially impacting neuromotor development, and the exclusion of cardiac or neurological causes that might lead to generalized seizures. A retrospective review of patient records was conducted, involving the collection of data including the age at the onset of the first seizure, gender, categorization of seizures as cyanotic, pallid, or mixed type, the frequency of seizures up to the point of admission, vitamin D levels, and other pertinent laboratory findings. Additionally, all patients attending the pediatric cardiology polyclinic underwent echocardiographic examinations.

### Control group

Patients who visited the Pediatric Polyclinic of Adiyaman University Training and Research Hospital between December 2019 and October 2022, and did not have any systemic diseases, were selected for this study.

Demographic and laboratory information of these patients was documented. The criteria for inclusion in this group required the absence of congenital heart conditions, epilepsy, or any disorders influencing vitamin D metabolism (such as rickets, chronic kidney failure, or calcium metabolism disorders).

### Laboratory parameters

Complete blood count, vitamin D, calcium phosphorus, alkaline phosphatase, ferritin, and iron binding capacity were investigated.

### Statistical Analysis

SPSS named software (IBM, version 21.0, Chicago, IL, USA) package program was employed to carry out the statistical evaluation of the data achieved from this study. Percentages (%) were used to express categorical data and a chi-square test was conducted to compare them. The Kolmogorov-Smirnov test was applied to assess the normality of data distribution. Continuous data that did not have a normal distribution were presented as medians (minimum and maximum), and the Mann-Whitney U test was used to compare them. The results were regarded as statistically significant in the case of p-values of less than 0.05.

### Ethics

All procedures conformed with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its subsequent modifications or equivalent ethical standards. Ethical approval was granted by the institutional review board of Adiyaman University (date: 07/11/2022, no: 2022/8-12).

### Results

The records of 98 patients, who visited the Pediatric Neurology and Pediatric Cardiology polyclinics of Adiyaman University Training and Research Hospital between December 2019 and October 2022 and were diagnosed with BHS, were retrospectively analyzed. Fifty-two patients with neurological or cardiological developmental risk factors or incomplete file data were excluded. Therefore, the study was conducted with a cohort of 46 children diagnosed with BHS, whose laboratory results were assessed, and a healthy control group of 53 individuals. No significant differences were observed in terms of sex or age between these two groups. The study group included 46 patients, with 27 girls (58.6%) and 19 boys (41.3%) (F/M=1.4). The average age at the onset of the first BHS was  $23.3 \pm 14.4$  months. The ages of the patients ranged from five to 78 months (**Table 1**). Within the patient cohort, 39 (84.8%) were diagnosed with cyanotic syncopal attacks, three (6.5%) with pallid-type spells, and four (8.7%) with mixed-type spells (**Table 2**). Regarding frequency, three (4%) patients experienced 1-4 attacks annually, 15 (33%) experienced 1-4 attacks monthly, 15 (33%) experienced 1-4 attacks weekly, and four (8%) experienced 1-4 attacks daily, while nine (22%) had experienced their first attacks (**Table 3**).

**Table 1.** A comparison of sex and age findings between the patient and control groups

	Patient group n=46	Control group n=53	P value
Sex (F/M)	27/19	26/27	0.42
Age (mean $\pm$ SD), in months	$23.3 \pm 14.4$	$23.2 \pm 15.3$	0.99

**Table 2.** BHS type

	Patient group n=46
Cyanotic	39 (84.8%)
Pallid	3 (6.5%)
Mixed	4 (8.7%)

**Table 3.** Frequency of BHS

Attack frequency	Patient group n=46
1-4 a year	3 (4%)
1-4 a month	15 (33%)
1-4 a week	15 (33%)
1-4 a day	4 (8%)
First time	9 (22%)

A significant correlation was not observed between BHS and vitamin D deficiency ( $p>0.05$ ); however, noteworthy connections were established with vitamin B12 ( $p=0.04$ ) and ferritin ( $p=0.01$ ) levels. Laboratory measurements for both groups are outlined in **Table 4**. All echocardiographic assessments conducted on the patient cohort at the pediatric cardiology polyclinic yielded results within the normal ranges.

**Table 4.** A comparison of the patient and control groups' laboratory findings

	Patient group n=46	Control group n=53	P value
Hemoglobin (g/dl)	11.7 ± 1.33	12.39 ± 0.95	<0.05
Hematocrit (%)	35.5 ± 3.8	37.7 ± 3.2	0.12
MCV (fL)	76.2 ± 8.7	75.5 ± 6.5	0.82
RBC 10 <sup>6</sup> /uL	4.7 ± 0.5	4.9 ± 0.9	0.07
MPV (fL)	6.3 ± 1.1	6.4 ± 1.4	0.74
Fe (ug/dl) (median: min-max)*	51:18-128	42: 15-128	0.24
Serum iron binding capacity (155 - 300 ug/dl)	277 ± 70	276 ± 84	0.96
Ferritin (11-300 ng/ml) (median: min-max)*	14.8:1-81	18:1-128	0.01
Serum B12 (189 ng/ml) (median: min-max)*	241:82-549	314:62-768	0.04
25-Hidroxy Vitamin D (10-80 ng/ml) (median: min-max)*	28.2:8.6-74	33:16-153	0.19

\*Non-normally distributed values were expressed as median, minimum, and maximum. All normally distributed values were expressed as mean ± standard deviation.

## Discussion

The prevalence of BHS is around 4-5%, although a study from Türkiye reported a rate of 3.6%.<sup>6,7</sup> The typical age of BHS onset falls between six and 18 months. Generally, these episodes tend to cease by around five years of age.<sup>8</sup> However, Goroya et al. reported that attacks persisted in a patient aged 8.5 years.<sup>9</sup> The age range in the present study was between 5-78 months. Our findings are consistent with the literature, and the mean age at diagnosis was 18 months. BHS are more prevalent in boys. Işıkay reported that boys represented 63.9% of cases.<sup>10</sup> In the present study, female gender is predominant. The predominant form of BHS is the cyanotic type, constituting most cases.<sup>11</sup> Işıkay observed cyanotic-type BHS in 86.1% of instances, whereas Aydın et al. reported a prevalence of 56.1%.<sup>10,12</sup> Similarly, the current study exhibited cyanotic-type BHS as the predominant category, comprising 84.8% of cases. Literature suggests that these episodes can manifest with diverse frequencies, ranging from multiple occurrences in a day to once a month, or even rarely, once a year.<sup>13</sup> In the present study, most attacks occurred weekly or 1-4 times a month, with a notable rate of 15%. These findings are compatible with others.<sup>10</sup>

Several studies, the majority from Türkiye, have suggested that a relationship exists between anemia and BHS in babies.<sup>14</sup> In their prospective study, Mocan et al. reported iron deficiency in 63 (69%) out of 91 patients aged 6-40 months.<sup>2</sup> Additionally, Yılmaz et al. and Tomoum et al. also reported significantly lower mean hemoglobin concentrations in patients with BHS compared to control groups.<sup>15,16</sup> Both iron deficiency and anemia play roles in the underlying mechanisms of BHS. Iron's involvement in catecholamine metabolism and neurotransmitter functioning has been acknowledged for a considerable time.<sup>17</sup> Its importance extends to regulating neurological processes, as it can impact the levels of monoamine oxidase in the brain.<sup>18</sup> Notably, this enzyme oversees various brain functions, and its deficiency may adversely affect them. However, very

few studies have investigated vitamin B12 levels in patients undergoing BHS. Two studies, one by Özçora et al. and the other by Arslan et al., found no significant association between vitamin B12 levels and BHS.<sup>19,20</sup> However, a statistically significant association was observed in the present study. Researchers have suggested that vitamin D affects erythropoiesis. Research has proposed a potential link between vitamin D deficiency and increased susceptibility to anemia, lower mean hemoglobin levels, and a higher usage of erythrocyte-stimulating agents. Hesamifar et al. demonstrated that rising iron deficiency anemia and decreased levels of serum calcium and vitamin D in children under five were connected to the occurrence of BHS.<sup>21</sup> In order for vitamin D to be actively synthesized by ultraviolet (UV) radiation, the light must reach the inner layers of the skin. In addition, the synthesis of vitamin D also takes place in an indirect way.<sup>22</sup> In darker-skinned people, the synthesis of indirect vitamin D is lower due to the relatively thicker melanin pigment of the skin. As the majority of people living in south-eastern Anatolia are dark-skinned and prefer to wear long clothes that cover their skin in winter, indirect vitamin D synthesis cannot be sufficiently realized. Vitamin D therefore needs to be nutritionally supplied. Vitamin D preparations (400U/3 drops) are provided by the Ministry of Health and distributed by family physicians. Notably, routine vitamin D administration in all infants aged 0-1 year is a public health policy in Türkiye. The prevalent use of the well-absorbed oil form of vitamin D might potentially explain the absence of a discernible link between vitamin D levels and BHS in our study. While the current study did not identify a statistically significant correlation between vitamin D levels and BHS, our research holds value due to the limited number of studies on this topic. However, further investigations involving larger patient cohorts are now warranted. Another study conducted in Türkiye explored the hypothesized relationship between serum calcium and magnesium levels and BHS. However, no statistically significant relationship was identified. Vitamin D levels were not examined in that study.<sup>23</sup> The primary limitations of this study lie in the relatively small patient sample size and the retrospective and hospital-based nature of the data collection.

The clinical characteristics of BHS were described in the pediatric literature in the XIX<sup>th</sup> and early XX<sup>th</sup> centuries.<sup>24</sup> Most of the studies on BHS have been conducted in Western countries. In the study of DiMario and Sarfarazi; the results show that consanguineous marriage is an important risk factor.<sup>25</sup> Consanguineous marriages are also common in the city where this study was carried out. Although it is easy to diagnose, there is still a lack of data in developing countries. The prevalence of BHS in children living in southern Turkey is estimated to be 3.8%.<sup>26</sup> It is well known that iron is the most important element in the pathophysiology of BHS. Iron therapy was recommended for BHS with or without anemia by Gürbüz et al.<sup>27</sup> In addition, both iron and vitamin B12 supports were emphasized in the study conducted by İbili and Çavuşoğlu in Afyonkarahisar province.<sup>28</sup> In our country, Çarman et al. in Eskişehir province, Işıkay in Gaziantep province and Aydın et al. in Adıyaman province have carried out studies on BHS.<sup>7,10,12</sup>

In conclusion, this article explored the potential links between common nutritional deficiencies specifically, iron, vitamin B12, and vitamin D in Türkiye and their potential relationship with BHS. Moreover, given the limited research on this topic, we sought to emphasize the potential influence of vitamin D deficiency on BHS. The study findings suggest no significant correlation between low vitamin D levels and BHS, which generally have a favorable prognosis. Nonetheless, routine assessment of these factors is advisable due to the possible associations with iron deficiency anemia and vitamin B12 levels.

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The author has no conflict of interest to declare.

### **Ethical Approval**

Ethics Committee of Adıyaman Universty (date: 07/11/2022, no: 2022/8-12)

## Author Contributions

Rojan İpek: Idea/concept, design, data collection and processing, literature review, article writing, critical review, references and fundings.

Celal Varan: Idea/concept, control/supervision, data collection and processing, analysis or interpretation, article writing, critical review, references and fundings.

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