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Original Article

Transient loss of consciousness: Neurally-mediated syncope, psychogenic syncope or epilepsy? A cross-sectional study

Geçici bilinç kaybı: nöral aracılı senkop, psikojenik senkop veya epilepsi? Kesitsel bir çalışma

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ABSTRACT

Aim: This study aimed to define important clinical and laboratory features that may be useful in the differential diagnosis of pediatric patients who presented with temporary loss of consciousness and in whom cardiac causes had been excluded, especially in the differentiation of convulsive syncope and epileptic seizure.
Methods: The records of patients presenting with temporary loss of consciousness and in whom cardiac causes had been excluded, were retrospectively evaluated. All patients were grouped according to their diagnosis and the data were evaluated comparatively.
Results: Six-hundred-and-twelve patient files were evaluated, and 350 patient files were included in the study. 68.6% of the patients were diagnosed with vasovagal syncope, 13.1% were diagnosed with psychogenic pseudosyncope and 18.2% of the patients were diagnosed with epilepsy. In addition, compared to other subgroups, the patients in the epilepsy group were younger ($p<0.001$), the total number of attacks was lower ($p<0.001$), the attacks lasted longer ($p<0.001$), post-attack symptoms were more common ($p<0.001$), and urinary incontinence and motor movements were more frequent ($p<0.001$).
Conclusion: The incidence of epilepsy was found to be significantly higher than expected in the pediatric patients presenting with transient loss of consciousness without cardiac reasons. Patient age, number and duration of attacks, presence of urinary incontinence and motor movements may also be important in the differential diagnosis of transient loss of consciousness. This study indicates that the management of transient loss of consciousness needs to be tailored to pediatric patients.

Keywords: Epilepsy, syncope, syncope unconsciousness, urinary incontinence, vasovagal

ÖZ

Amaç: Bu çalışmada, geçici bilinç kaybı ile başvuran ve kardiyak nedenler dışlanmış pediatrik hastaların ayırıcı tanısında, özellikle konvülziv senkop ve epileptik nöbet ayrımında yararlı olabilecek önemli klinik ve laboratuvar özelliklerin tanımlanması amaçlanmıştır.
Yöntem: Geçici bilinç kaybı ile başvuran ve kardiyak nedenler dışlanan hastaların dosyaları geriye dönük olarak incelendi. Tüm hastalar tanılarına göre gruplandırıldı ve veriler karşılaştırmalı olarak değerlendirildi.
Bulgular: Altı yüz on iki hasta dosyası değerlendirildi ve 350 hasta dosyası çalışmaya dâhil edildi. Hastaların %68,6'sına vazovagal senkop, %13,1'ine psikojenik psödosenkop ve %18,2'sine epilepsi tanısı konuldu. Ayrıca epilepsi grubunda diğer alt gruplara göre; hastaların daha küçük yaşta olduğu ($p<0.001$), toplam atak sayısının daha az olduğu ($p<0.001$), atakların daha uzun sürdüğü ($p<0.001$), atak sonrası semptomların daha uzun sürdüğü ($p<0.001$), idrar kaçırma ve motor hareketlerin daha sık görüldüğü saptandı ($p<0,001$).
Sonuç: Bu çalışma ile geçici bilinç kaybı ile başvuran kardiyak nedenler dışlanmış pediatrik hastalarda epilepsi insidansı beklenenden oldukça yüksek bulundu. Geçici bilinç kaybının ayırıcı tanısında hastaların yaşı, atak sayısı ve süresi, idrar kaçırma ve motor hareketlerin varlığı açısından sorgulanması önemlidir. Bu çalışma, geçici bilinç kaybı yönetiminin pediatrik hastalara göre uyarlanması gerektiğini açıkça ortaya koymaktadır.

Anahtar kelimeler: Bilinç kaybı, epilepsi, senkop, üriner inkontinans, vazovagal senkop

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INTRODUCTION

Transient loss of consciousness (TLOC) is a common problem in children and adolescents, given the fact that approximately 15% of the population experiences it at least once before the age of 18. Syncope can be defined as TLOC and postural tone due to cerebral hypoperfusion (1).

These patients are often referred to pediatric cardiology and neurology clinics for recurrent syncopal episodes and many tests are performed on these patients (2,3).

The majority of syncope in the pediatric population is related to neurally-mediated syncope (NMS). Vasovagal syncope (VVS) is the most frequent form of NMS (1).

Importantly, the diagnosis of epilepsy can be made in some of the children who are being evaluated for syncope. Therefore, the distinction between NMS and other more serious diseases (eg epilepsy and cardiac diseases) should be carefully made in patients presenting with syncope-like symptoms (4).

Detailed clinical guidelines for syncope have been published. However, there are still difficulties encountered in the diagnosis and patient management (5,6). Many unnecessary tests are being performed to exclude rare important conditions (epilepsy, cardiac causes), and all patients who experience temporary changes in consciousness are referred to the pediatric cardiology and pediatric neurology departments (4).

The difficulty of the differential diagnosis of epilepsy can be better understood when it is considered that convulsive activity can also occur in patients with syncope. It has been reported that 74,000 patients were misdiagnosed with epilepsy in England in 2007 and the coexistence of convulsive syncope and epileptic activity was partly responsible for this situation (7).

This study aimed to define important clinical and laboratory features that may be useful in the differential diagnosis of pediatric patients who presented with temporary loss of consciousness and in whom cardiac causes had been excluded, especially in the differentiation of convulsive syncope and epileptic seizure.

MATERIALS AND METHODS

This is a retrospective study conducted in the department of pediatric neurology. Ethical approval for the study was obtained from the Ethics Committee Number 1 of the Ankara City Hospital (E1-20-577). The study was conducted in accordance with the Declaration of Helsinki.

The files of all pediatric patients who were admitted to pediatric neurology clinics due to TLOC were evaluated. All the patient files evaluated in the study belonged to patients managed and treated by the authors. The inclusion periods were therefore varied.

Files of patients who did not undergo an adequate cardiological evaluation and who were diagnosed or suspected of cardiac syncope were excluded from the study. In addition, files of the patients with known neurological disorders or with insufficient hospital records were also excluded from the study.

Demographic and clinical characteristics and laboratory results of the patients were obtained from the files (Table 1, Table 2).

The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society 2017 guidelines were used for syncope classification (1).

Initial and serial awake and sleep electroencephalogram (EEG) recordings (obtained with Nihon Kohden -Tokyo, Japan- and Neurosoft -Ivanovo, Russia- using 18 channels with the scalp electrodes distributed according to the 10-20 system) of patients who had motor movements during the episode or post-ictal consciousness changes or had first- or second-degree relatives with epilepsy, were reassessed by two pediatric

neurologists who were blinded to the patients' clinical data. EEG recordings less than 20 minutes were not included in the study.

Normally distributed variables between two independent groups were compared using the Student's t-test. The Mann-Whitney U test was used for the comparisons of non-normally distributed data. Differences in the normally distributed variables among more than two independent groups were analyzed by one-way ANOVA. The Kruskal-Wallis test was used for comparisons of the non-normally distributed data. The post hoc least significant difference or Conover's non-parametric multiple comparison tests were used to determine which group differed from the others.

RESULTS

Six-hundred-and-twelve patient files were evaluated. Three-hundred-fifty patient files were included in the study, considering the exclusion criteria (Figure 1). The mean age of the patients was 147.0 (±50.2) months old and 196 of the patients were girls (56.0%). The neurological examination of all patients was unremarkable.

The patients were categorized into three groups: Vasovagal syncope (VVS), epilepsy and psychogenic pseudosyncope (PPS), and their clinical and laboratory results are presented in Table 1.

Among the patient groups, the epilepsy patients were the youngest, while the PPS patients were

Table 1. Demographic data and clinical findings of the patients.

	VVS (n: 240)	Epilepsy (n: 64)	PPS (n: 46)	P-value
Age (years) (n, %)*				
7–9	63 (26.3%)	23 (35.9%)	1 (2.2%)	
10–14	107 (44.6%)	27 (42.2%)	22 (47.8%)	**0.002[b]**
>15	70 (29.2%)	14 (21.9%)	23 (50%)	
Gender (female/male) (n)*	130/110	26/20	40/24	0.489
Family history of epilepsy (n, %)*	19 (7.9%)	18 (28.1%)	12 (26.1%)	**<0.001[a,b]**
Number of attacks (n, %)*				
1	94 (39.2%)	25 (39.1%)	11 (23.9%)	
2	85 (35.4%)	28 (43.8%)	16 (34.8%)	**<0.001[a,b,c]**
3	38 (15.8%)	8 (12.5%)	2 (4.3%)	
>3	23 (9.6%)	3 (4.7%)	17 (37.0%)	
Time between episodes (days, mean ± SD)[β]	10.6 ± 6.2	24.2 ± 8.7	2.3 ± 1.3	**<0.001[a,b,c]**
Relation with position (n, %)*				
Standing for long periods	175 (72.9%)	7 (10.9%)	6 (13,0%)	
During physical activity	4 (1.7%)	9 (14.1%)	8 (17.4%)	**<0.001[a,b,c]**
Sitting	11 (4.6%)	12 (18.8%)	2 (4.3%)	
Lying down	18 (7.5%)	13 (20.3%)		
Independent of position	32 (13,3%)	23 (35.9%)	30 (65.2%)	
Triggers with emotional and painful stimulus*	203 (84.5%)	3 (4.7%)	40 (86.9%)	**<0.001[a,c]**
Prodromal symptoms (n, %)*	209 (87.1%)	22 (34.4%)	22 (47.8%)	**<0.001[a,b,c]**
Unknown	23 (9.6%)	14 (21.9%)		
Duration of syncopes (n, %)*				
>2 min	8 (10.3%)	24 (75.0%)	7 (35.0%)	**<0.001[a,b,c]**
<2 min	70 (89.7%)	8 (25.0%)	13 (65.0%)	
Urinary incontinence (n, %)*	8 (3.3%)	24 (37.5%)	1 (2.2%)	**<0.001[a,c]**
Seizure-like motor movements (n, %)*	33 (13.8%)	44 (68.8%)	15 (32.6%)	**<0.001[a,c]**
Change in skin color (n, %)*				
Pallor	140 (58.3%)	-	-	
Cyanosis	14 (5.8%)	25 (39.1%)	8 (17.4%)	**<0.001[a,b,c]**
Post-episodic symptoms (n, %)*	24 (10.0%)	35 (54.7%)	9 (19.6%)	**<0.001[a,b,c]**

*Categorical data were described as number of cases (%) and compared using the Pearson's chi-square test or fisher's exact test. * Continuous variables were expressed as either the mean ± SD or the median, and compared using the Kruskal Wallis test[β]. The Conover-Inman test was performed for binary comparisons among the groups and statistical significance was accepted as P < 0.05. Significant differences were found between: a) neurally mediated syncope vs. epilepsy, b) neurally mediated syncope vs. Psychogenic pseudosyncope (PPS) and c) PPS vs. epilepsy. Statistically significant P-values are represented by bold font. VVS:Vasovagal syncope; PPS: Psychogenic pseudosyncope.*

the oldest (p=0.001). The rate of positive family history for epilepsy was similar in the epilepsy and PPS groups (28.1% and 26.1%, respectively), while it was very low in the VVS group (7.9%, p<0.001).

When the total number of episodes (syncope or seizures) since admission was evaluated, it was seen that 95.4% of the epilepsy group, 90.4% of the VVS group, and only 63.3% of the PPS group had three or fewer episodes (p<0.001).

All 64 patients who were diagnosed with epilepsy had abnormal EEG recordings. Considering the clinical features and EEG findings, 57 patients were diagnosed with generalized epilepsy (89.1%), while the remaining seven with focal epilepsy. However, only 35 of the patients who were diagnosed with epilepsy had postictal confusion (54.7%). The remaining patients had suspected convulsive syncope but were diagnosed with epilepsy based on their EEG recordings.

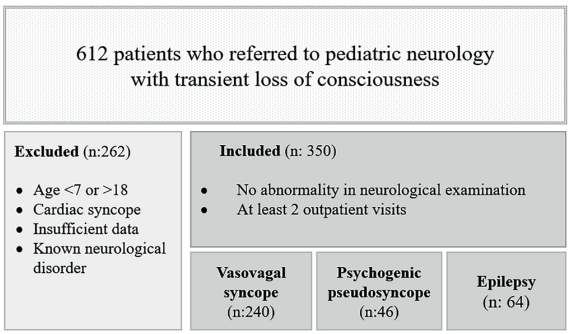

Figure 1. Study flowchart.

Post-episodic symptoms were significantly more common in the epilepsy group (p<0.001). Standing posture during the episode was observed in 72.9% of the patients in the VVS group, and in 10.9% and 13% of the patients in the epilepsy and PPS groups, respectively (p<0.001). VVS was triggered by an emotional or painful stimulus in 84.5% of patients, which is significantly more common in the other groups (p<0.001). The effect of a hot environment was not statistically significant among groups.

In the PPS and VVS groups, episodes were shorter than two minutes in 65% and 89.7% of the patients, respectively, while epileptic seizures were significantly longer than two minutes in 75% of the epilepsy group (p<0.001). Urinary incontinence and motor movements were more frequent during epileptic seizures (p<0.001).

Seizure-like motor movements were more common in the epilepsy group (p<0.001) but these movements were also reported in 32.6% of the PPS patients. Pallor was more common in the VVS group (p<0.001), while cyanosis was more common in the epilepsy group (p<0.001). Only eight patients had changes in skin color in the PPS group (17.4%). Lip and tongue injuries or head trauma during episodes were statistically similar among groups, which were reported in 25% of the epilepsy group, 14.1% of the VVS group, and 10% of the PPS group.

Table 2. Laboratory results of the patients in each group.

	VVS (n: 240)	Epilepsy (n: 64)	PPS (n: 46)	P-value
Hemoglobin (mean ± SD)$^{\beta}$ (mg/dl)	13.5 ± 1.6 (13.60)	13.8 ± 1.1 (13.25)	13.2 ± 1.3 (13.90)	0.809
Hematocrit (mean ± SD)$^{\beta}$ (%)	41 ± 3.9 (38.6)	40.6 ± 3.1 (37.4)	42.1 ± 4.7 (39.4)	0.901
MCV (mean ± SD) $^{\beta}$ (fl)	89.4 ± 68.6 (82.6)	85.6 ± 4.5 (84.9)	82.1 ± 3.9 (79.7)	**0.015**^{b,c}
RDW (mean ± SD)$^{\beta}$ (fl)	14.1 ± 1.3 (13.8)	13.8 ± 0.7 (13.4)	14.7 ± 1.1 (14.4)	**0.011**^{a,c}
Iron (mean ± SD)$^{\beta}$ (µg/dl)	65.2 ± 36.8 (57.0)	71.3 ± 27.7 (71.0)	60.2 ± 36.6 (66.0)	0.411
Ferritin (mean ± SD)$^{\beta}$ (ml/ng)	22.3 ± 17.9 (16.9)	18.7 ± 12.1 (20.0)	9.4 ± 9.3 (7.3)	**0.018**^{a,c}
TSH (mean ± SD)$^{\beta}$ (µU/ml)	2.4 ± 1.6 (2.1)	2.6 ± 1.0 (2.7)	1.6 ± 0.7 (1.5)	**0.020**^{c}
Free T4 (mean ± SD)$^{\beta}$ (pg/ml)	1.3 ± 0.5 (1.2)	3.9 ± 5.6 (1.4)	1.3 ± 0.2 (1.4)	0.089
Vitamin B12 (mean ± SD$^{\beta}$ (pg/ml)	351.1 ± 183.6 (309.0)	340.3 ± 139.3 (280.0)	315.8 ± 90.4 (289.5)	0.573

Continuous variables were expressed as either the mean ± SD or the median, and compared using the Kruskal Wallis test $^{\beta}$ The Conover-Inman test was performed for binary comparisons among the groups and statistical significance was accepted as P < 0.05. Significant differences were found between: a) VVS vs. epilepsy, b) VVS vs. PPS, and c) epilepsy vs. PSS. Statistically significant P-values represented by bold font. MCV: mean corpuscular volume; PPS: Psychogenic pseudosyncope; RDW: red cell distribution width. TSH: thyroid stimulating hormone; VVS:Vasovagal syncope.

Table 2 summarizes the results of the laboratory findings. Ferritin levels were significantly lower in the PPS group and highest in the VVS group (p=0.018).

Cranial magnetic resonance imaging (MRI) was performed in 176 patients to determine the structural etiology of TLOC. However, none of these findings could be associated with the clinical findings.

DISCUSSION

Loss of consciousness in pediatric patients is a major source of concern for the patients and their families, especially until life-threatening causes are ruled out (8).

Clinical guidelines for syncope in pediatric patients should be used routinely (5,6). In a retrospective study, it was shown that the patients were evaluated more systematically and effectively after the use of the diagnostic approach algorithm for syncope in the pediatric emergency department (9). Effective use of guidelines in the emergency department in clinical practice can facilitate patient management.

The most striking finding in our study was that the diagnosis of epilepsy was seen at a rate of 18%. A study on pediatric patients with unknown origin of syncope showed that 4 out of 18 patients (22.2%) were diagnosed with epilepsy at long-term follow-up (10).

All the patients who were diagnosed with epilepsy in our cohort had abnormal EEG recordings. This stresses the importance of the EEG in distinguishing convulsive syncope from epileptic seizure. The American Heart Association recommends EEG recording and monitoring of vital signs at the same time as the tilt test, but does not recommend routine EEG recording in patients whose medical history and physical examination does not indicate neurogenic etiology (1,6). A detailed history is crucial for the evaluation of patients with loss of consciousness. Since younger children may not be able to express the period prior to, during, and after the episode, and the lack of a witness can make it impossible to have a clear understanding of the situation.

Another important issue is how to distinguish convulsive syncope from epileptic seizures based on clinical findings. Although myoclonic jerks in the extremities and locked jaw are common in neurogenic syncope, similar findings can also be observed in other groups due to cerebral hypoxia, which is defined as convulsive syncope. In a previously mentioned study, in which simultaneous EEG recordings were performed with the tilt test, myoclonic jerk was observed in the upper extremities in 25% of the patients during the episode (11). In patients with motor movements, whether these movements occur before or after loss of consciousness is a guide to diagnosis. While motor movements are observed after loss of consciousness in convulsive syncope, motor movements begin simultaneously with loss of consciousness in epileptic seizures (8). Capturing this detail in the patient's history may assist the diagnosis.

Postictal confusion, which is a feature of epilepsy but is absent in convulsive syncope, can also be seen as a key point in making this distinction. One of the interesting findings of our study was that only 54.7% of the epilepsy patients had postictal confusion. The remaining patients were thought to have convulsive syncope initially but were finally diagnosed with epilepsy based on the EEG recordings.

As a result, our study suggests that EEG has an important place in the management of TLOC in the younger age group. For this patient group, it may be necessary to review the EEG indications for future guidelines.

On the other hand, we found that urinary incontinence was significantly higher in the epilepsy group compared to the other groups. The rate of urinary incontinence in non-epileptic patients was found to be around 3%. Additionally,

in another retrospective study, the incidence of urinary incontinence in patients with psychogenic nonepileptic seizures was found to be 12% (12). In our study, this rate was found to be as high as 37.5% in epileptic patients. A pooled analysis of data from the literature showed that the presence of urinary incontinence is not indicative of whether an episode is epileptic (13). However, this may be due to the fact that only patients with loss of consciousness accompanied by motor movements were evaluated in this study.

We found that the patients in the PPS group had significantly lower ferritin levels, lower MCV, and higher RDW. There is not enough information on this in the current medical literature.

Post-episodic neuroimaging was performed in 176 of the patients with a history of TLOC, however, imaging did not provide any specific findings in any of the patients. This again demonstrates that imaging does not contribute to the diagnosis in patients with TLOC and normal neurological examination (14).

The strength of our study is that the number of patients was statistically large enough to easily capture the differences. If the clinical features had been evaluated separately, significant differences between the main causes of TLOC could have been detected. However, the retrospective nature of the study limits the power of the information obtained. Long-term follow-up would be valuable to obtain more accurate clinical results.

In this study, patients between the ages of 7 and 18 with loss of consciousness were evaluated, and the incidence of epilepsy was found to be significantly higher than expected. This result indicates that the management of transient loss of consciousness needs to be tailored to pediatric patients.

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