

## ETIOLOGY OF SYNCOPE IN CHILDREN: HOW OFTEN SHOULD WE CONSIDER IT NEUROGENIC?

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*The most common paroxysmal non-epileptic events in children are syncopes, a sudden and temporary loss of consciousness provoked by stimuli, followed by the loss of postural tone and with complete recovery within seconds to minutes. The aim of this study was to determine the causes, provocations, diagnostic procedures and classification of syncopes in children and adolescents. Data on patients admitted because of syncope to our Neuropediatric Unit during a 2-year period (January 2005 to December 2006) were retrospectively analyzed. Out of 326 children with non-paroxysmal events, 68 children diagnosed with syncope were chosen for further analysis. The mean age of study children (female 70% and male 30%) was 13.67 years. About 70% of children were admitted urgently. Two or more syncopal attacks were recorded in 49% of children. Laboratory, neurologic and cardiologic procedures were performed, depending on history and physical examination. The causes of syncopal attacks were vasovagal, situational, orthostatic hypotension, spasm of the right vertebral artery, psychogenic, canal for vertebral artery, and epilepsy. In 5.9% of cases, syncopal attacks remained unclassified. The most common syncope in hospitalized children was neurocardiogenic. The diagnosis was mostly based on disease history and physical examination. EEG and follow up confirmed epilepsy in two children.*

Descriptors: SYNCOPE – classification, diagnosis; CHILD; SYNCOPE, VASOVAGAL

### INTRODUCTION

Syncope refers to the loss of consciousness due to decreased cerebral perfusion, mainly in the brainstem reticular activating system and cerebral cortex. Syncope is a common problem accounting for 3% of emergency department visits, 1%-6% of hospital admissions and affecting 6 per 1,000 people per year (1-3). Syncope is very rare before six years of age and about one of five children has syncope before five years of age (4, 5). It is estimated that 5% to 15% of children and adolescents have syncope between 8 and 18 years of age. The incidence of syncope peaks in adolescents aged 15-19 years (4, 5). Syncope tends to be recurrent

in 35% of patients during the first year. In children and adolescents, syncope rarely indicates the presence of serious cardiovascular disease. It usually reflects either an individual or a familial predisposition to common faint. The incidence of neurocardiogenic syncope was found to be higher in females than in males (4).

The pathophysiology of syncope can be various. Neurocardiogenic syncope refers to the following subtypes or conditions: neurogenic syncope, micturition, coughing, swallowing, carotid sinus, reflex syncope, orthostatic syncope (syndrome of postural orthostatic tachycardia), autonomic dysfunction, multiple systemic atrophy, and poor functioning of drainage, migraine, and hypoglycemia (6). Neurogenic syncope, previously termed vasovagal syncope, is the most frequent type and it is usually known as common faint. It is caused by a sudden decrease in blood pressure, temporarily causing dizziness (presyncope) or a brief loss of consciousness (syncope). The

Bezold-Jarisch reflex, which is an extreme or overshoot of a normal response to hypotension, is a postulated cause (7).

Cardiogenic syncope due to dysrhythmias results in decreased cardiac output. These dysrhythmias include supraventricular tachycardia (SVT), ventricular tachycardia (VT), ventricular fibrillation, and extreme forms of bradycardia (e.g., heart block).

Syncope in a patient with documented pre-excitation (i.e. Wolff-Parkinson-White syndrome) can be serious, suggesting a risk of sudden death. SVT usually produces some type of warning, such as palpitations, dizziness, or both, before causing syncope. Patients with VT may present with palpitations, dizziness, or both.

History and physical examination are the most specific and sensitive ways to evaluate syncope. Laboratory findings, further neurologic and cardiologic evaluation are performed depending on data obtained by history and physical examination.

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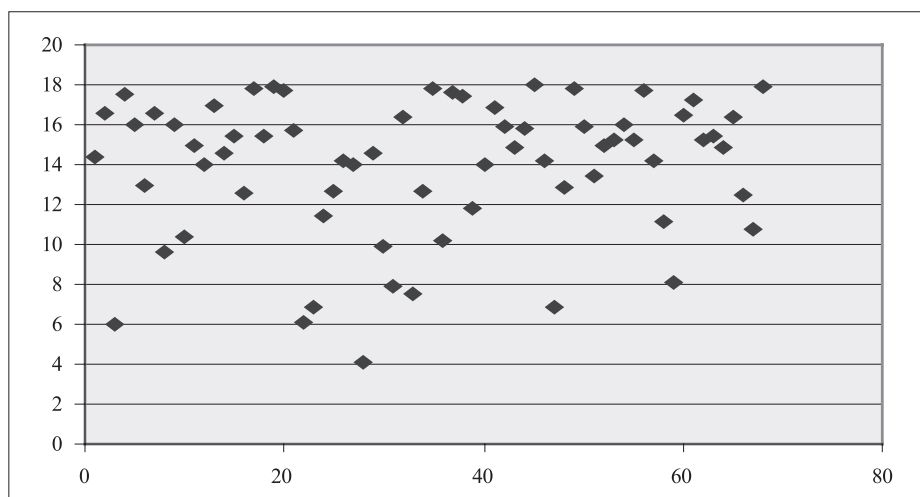
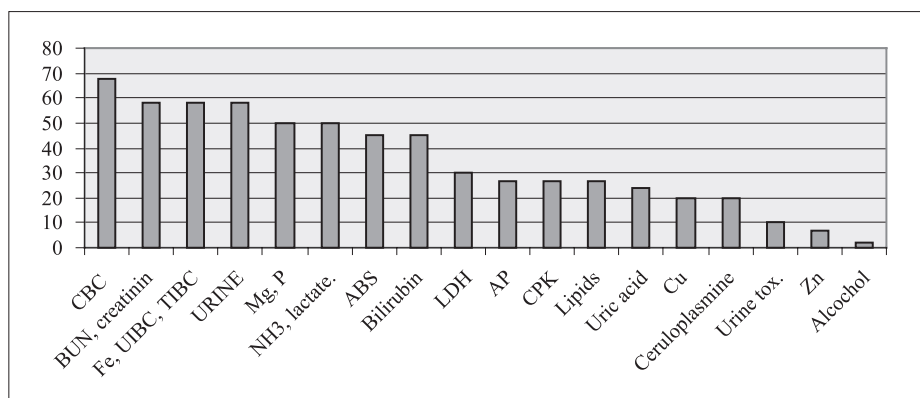


Figure 1. Age distribution of 68 children with syncope  
Slika 1. Raspodjela po dobi u 68-ero djece sa sinkopom



CBC – complete blood count; BUN – blood urea nitrogen; Fe – iron; Mg – magnesium; P – phosphorus; NH<sub>3</sub> – ammonium; ABS – acid-base status; LDH – lactate dehydrogenase; AP – alkaline phosphatase; CPK – creatine phosphokinase; Cu – copper; Zn – zinc.

CBC – kompletna krvna slika, BUN- urea, Fe – željezo, Mg - magnezij, P- fosfati, NH<sub>3</sub>- amonijak, ABS-acidobazni status, LDH – laktat dehidrogenaza, AP alkalna fosfataza, CPK – kreatin fosfokinaza, Cu – bakar, Zn-cink.

Figure 2. Number of children submitted to selected laboratory tests (n=68)  
Slika 2. Broj djece s obavljenim pojedinim laboratorijskim pretragama (n=68)

The aim of this study was to determine the causes, provocations, diagnostic procedures and classification of syncopes in children and adolescents.

#### PATIENTS AND METHODS

##### Patients

In this study, data on children admitted because of syncope and treated at our Neuropediatric Unit and Outpatient Neuropediatric Clinic were retrospectively analyzed. Out of 326 children hospitalized for non-paroxysmal events during a 2-year period (January 2005 to December 2006), 68 children diagnosed with syncope were chosen for further analysis using medical records on admission to Emer-

gency Department, letters of discharge and outpatient clinic files.

##### Methods

Data on children with syncope were analyzed according to age, sex, type of admission, prodromal symptoms, main symptoms, duration of syncope, etiology, recurrence, laboratory findings, neurologic and cardiologic evaluation.

Statistical methods used in the study depended on the sample size and type of variables. Means were calculated for continuous variables and frequencies for categorical variables. A cross-tab was applied to compare different variables and *P* values were calculated using Fisher's Ex-

Table 1. Characteristics of 68 children with syncope  
Tablica 1. Osobitosti 68-ero djece sa sinkopom

Characteristic/Značajka	n (%)
Sex/ Spol	
Male/muški	24 (35%)
Female/ženski	44 (65%)
Admission/Prijam	
Urgent/hitno	47 (70%)
Non-urgent/Dogovorno	21 (30%)
Number of syncopal episodes/ Broj sinkopa	
1	33 (49%)
2 or more/2 ili više	35 (51%)
Duration of unconsciousness/ Trajanje nesvjestice	
Few seconds/ nekoliko sekundi	51 (75%)
Few minutes/Nekoliko minuta	13 (19%)
>30 minutes/Više od 30 minuta	2 (3%)
No information/Nema podataka	2 (3%)
Part of the day at the time of syncope/Doba dana u vrijeme sinkope	
AM/Jutro	22 (32%)
PM/Popodne	9 (13%)
No information/Nema podataka	37 (55%)
Menstruation at the time of syncope/Menstruacija u vrijeme sinkope	
Girls with menstruation/Djevojčice s menstruacijom	31/44
Menstrual disorder/Poremačaj ciklusa	10/31 (32%)
Cause of syncopal attack/Uzrok sinkope	3/31 (10 %)

act Probability Test. *P* value less than 0.05 was considered statistically significant.

#### RESULTS

##### Characteristics of children with syncope

During a two-year period (January 2005 to December 2006), 326 children with paroxysmal events were hospitalized at Neuropediatric Unit, Sestre milosrdnice University Hospital Centre. About 20% (68/326) of children had syncope as the main diagnosis at admission. The mean age of 68 children with syncope was 13.67 (range 4.08-17.83) years, median 14.75 years (Figure 1). There were 24 (35%) male and 44 (65%) female children. Family history revealed psychiatric disorders in family members of four children, epilepsy in two, migraine in two and Parkinson's disease in one family member. Out of 35 school children, six were excellent, fourteen very good and five good pupils. One attended special school and four attended preschool, whereas no data were available for five children. Out of 44 girls, 31 had menstruation: 10/31 had painful and flush periods and in three

Table 2. *Etiology of syncope in 68 children*  
 Tablica 2. *Etiologija sinkopa u 68-ero djece*

Neurogenic syncope/Neurogena sinkopa	57 (83.8%)
Long-time standing/Dugotrajno stajanje	17
Sudden standing-up/Naglo ustajanje	2
Closed spaces – church, bus/ Zatvoreni prostori – škola, autobus	13
Pain + visual stimuli/Bol, vizualni stimulusi	9
Respiratory disease/Respiracijski infekt	4
Menstruation (pain)/Menstruacija (bol)	3
Emotional stress, anger/Emocionalni stres, ljutnja	2
Deprivation of sleep/Nedostatak sna	2
Situational/Situacijska	5
Psychogenic/Psihogeni	2 (3.0%)
Anxiety disorder/Anksiozni poremećaj	1
Hyperventilation/Hiperventilacija	
Sulcus of vertebral artery/Kanal vertebralne arterije	2 (2.9%)
Spasm of right vertebral artery/ Spazam desne vertebralne arterije	1 (1.5%)
Epilepsy/Epilepsija	2 (2.9%)
Unclassified/Nesvrstane	4 (5.9%)
Total/Ukupno	68 (100%)

of them menstruation was directly related to the actual syncopal episode (Table 1).

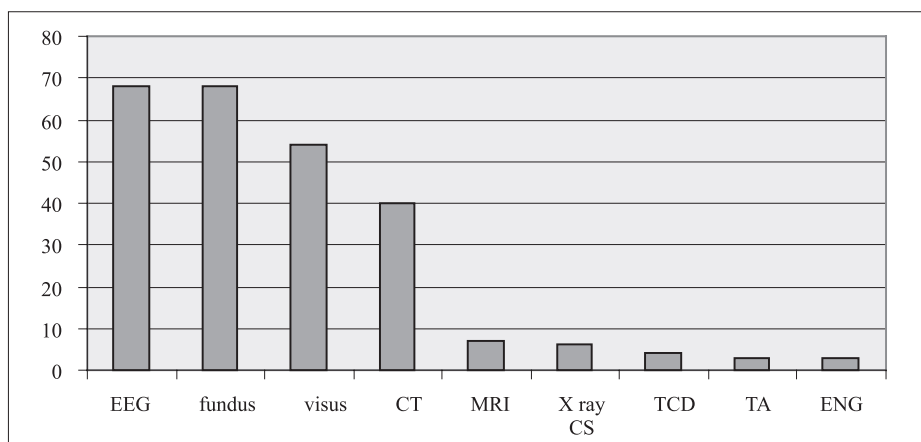
Urgent admission was the type of hospitalization in 70% of children, whereas 30% were hospitalized because of additional diagnostic evaluation of recurrent syncopal episodes (Table 1).

Two or more syncopal events were recorded in 51% of children, whereas 49% had their first syncopal episode at admission; 84% had no evident convulsions, whereas 16% described convulsions during syncope. Syncopal episodes mostly occurred in the morning and lasted for a few seconds (Table 1).

There was no significant sex difference according to urgent or non-urgent type of admission ( $P=0.1262$ , Fisher's exact test) or frequency of neurogenic syncope ( $P=0.5145$ , Fisher's exact test), but statistically significance was found in the recurrent nature of syncope in girls ( $P=0.0013$ , Fisher's exact test).

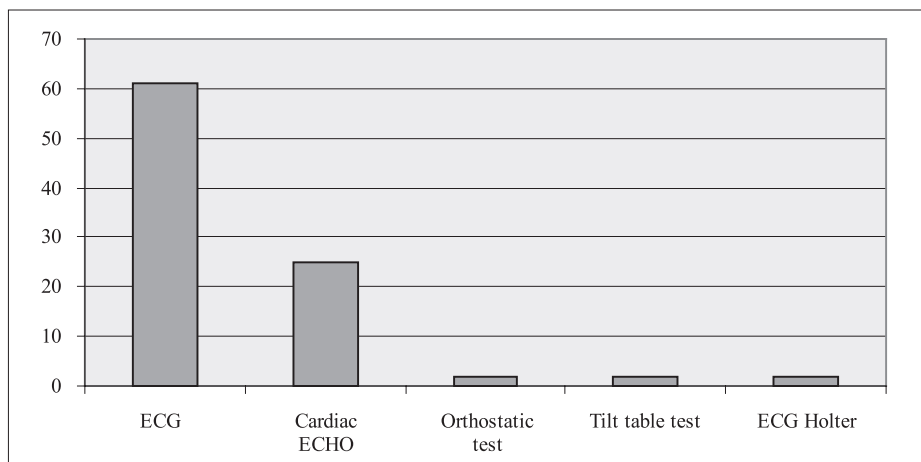
### Etiology of syncope

The etiology of syncope in 68 children is shown in Table 2. The cause of syncope



EEG – electroencephalography; CT – computed tomography; MRI – magnetic resonance imaging; x-ray CS – cervical spine x-ray; TCD – transcranial color doppler; TA – tonal audiogram; ENG – electronystagmogram. EEG elektroencefalogram, CT-kompjuterizirana tomografija, MRI – magnetska rezonancija, X-ray CS – rengenjska snimka vratne kralježnice, TCD- transkranijski obojeni dopler, TA- tonalni audiogram, ENG – elektronistagmogram

Figure 3. *Number of children submitted to neurologic evaluation (n=68)*  
 Slika 3. *Broj djece s učinjenim neurološkim pretragama (n=68)*



ECG – electrocardiogram; cardiac ECHO – echocardiography; ECG holter – Holter electrocardiogram. ECG – elektrokardiogram, cardiac ECHO – ehokardiografija, ECG holter – holter elektrokardiogram

Figure 4. *Number of children undergoing cardiologic evaluation*  
 Slika 4. *Broj djece s učinjenom kardiološkom obradom*

was successfully evaluated at first in 57/68 (83.8%) children using history of disease and physical examination at Emergency Department. Neurogenic syncope was the most frequent type. The reasons and precipitating factors for syncopal attack were long-time standing or sudden standing-up, closed spaces (church, tram or bus), pain and visual stimuli, respiratory disease, menstrual pain, emotional stress, anger, deprivation of sleep, and situational syncope. Two children had psychogenic syncope: one child had syncope due to hyperventilation and the other one had syncopal attacks due to anxiety. We put them separately, because, unlike other children, both of them required prolonged psychological support.

Further laboratory findings, neurologic and cardiologic evaluation helped us detect the cause of syncope in further 7/68 (10.3%) children, while the etiology remained unknown in 4/68 (5.9%) children. Biochemical findings performed in children with syncope are shown in Figure 2. Sideropenia was found in three children. Four children with indirect hyperbilirubinemia underwent genotyping for UDP-glucuronosyltransferase 1 (UGT1A1) gene polymorphism and Gilbert's syndrome was confirmed.

The proportion of children with neurologic evaluation is illustrated in Figure 3. Fundus and EEG were performed in all children. Two children fulfilled the International League Against Epilepsy (ILAE)

Table 3. Positive findings of selected diagnostic procedures in 68 children with syncope  
 Tablica 3. Pozitivni nalazi odabranih dijagnostičkih pretraga u 68-ero djece sa sinkopom

CT 6/40	MRI 2/7	EEG 4/68	Eye fundus/ Očna pozadina 1/68	ENG 1/3	X-ray of cervical spine/ radiološka snimka kralježnice 2/6
3/40 Inflammatory changes of paranasal sinuses/Upala paranasalnih sinusa 2/40 Cortical atrophy, asymmetric lateral ventricles/ Atrofija korteksa i asimetrične postranične komore 1/40 Calcifications nearby falx/ Kalcifikacije uz falks	1/7 Periventricular hypodensities/ Periventrikularni hipodenziteti 1/7 Pineal gland lipoma/ Lipom pinealne žlijezde	4/68 Dysrhythmic discharges/ Dizritmička izbijanja	1/68 Papillary pseudodema, nasal right/ Psuedoedem papile desno nazalno	1/3 Peripheral vestibular paresis (vestibular neuronitis)/ Periferna vestibularna pareza (vestibularni neuronitis)	2/6 Sulcus of vertebral artery/ Kanal vertebralne arterije

CT – computed tomography; MRI – magnetic resonance imaging; EEG – electroencephalography; ENG – electronystagmogram.

CT-kompjuterizirana tomografija, MRI-magnetska rezonancija, EEG-elektroencefalogram, ENG-elektronistagmogram

criteria for the diagnosis of epilepsy: one with EEG polysomnography two years after the initial diagnosis of syncope and another one because of repeated epileptic seizures.

Neuroimaging was performed in children with symptoms of the possible etiology of central nervous system or to exclude cranial lesions secondary to syncope. We used brain CT as the first step in urgent hospitalization in 40 children, and brain MRI for further evaluation in seven children, with standard protocol or with protocol for epilepsy. Positive neuroimaging findings are shown in Table 3. Only some of these findings could have been connected to the syncopal attacks (i.e. paranasal sinusitis). Studies such as x-ray, tonal audiogram/electronystagmogram (TA/ENG) and doppler of carotid and vertebralbasilar arteries were performed because of positive history of the possible cerebrovascular disorder or vertigo. Vestibular neuronitis and spasm of the right vertebral artery were found in one patient each, and sulcus of vertebral artery in two patients.

Cardiologic evaluation revealed only one child with interventricular conductive disturbances on ECG and normal echocardiography (ECHO) in all 25/68 children undergoing ECHO (Figure 4). Orthostatic test and tilt table test were posi-

tive in two children (Figure 5). Two children had normal findings on 24-h ECG Holter.

## DISCUSSION

### Characteristics of children with syncope

Characteristics of our study children with syncope were consistent with those reported from similar studies in pediatric population with syncope, especially considering female prevalence, average age of 15 years at the time of syncope and urgent admission (8, 9).

Characteristics of syncopal episodes in our children were also consistent with other studies in pediatric population, i.e. recurrent nature of syncope, short duration of syncopal episodes and neurally mediated syncope as the most frequent type of syncope (10, 11).

Recurrent nature of syncope in girls observed in this study suggests that female patients may be prone to experience syncopal episodes more easily than males. Women are more susceptible to orthostatic intolerance in warm conditions. Fluctuations of female sex hormones during menstrual cycle have been shown to have numerous effects on physiological parameters (12). The sex related recurrence of syncope was also observed in some other studies (7, 13-16). On the contrary, some

large studies showed higher rates of hospitalized men with syncope, especially due to orthostatic hypotension (17, 18).

Physical examination in our patients with simple faint demonstrated no abnormal physical findings. History and physical examination were the most specific and sensitive ways to evaluate syncope. The diagnosis is usually achieved by thorough history and physical examination in 50%-85% of patients (19-21).

Our patients had syncopal episodes mostly in the morning. Common faint or neuroregulatory syncope is more likely to occur in the morning, particularly after rising, or upon prolonged standing at any time of day (22).

### Etiology of syncope

Laboratory tests are usually performed because of suspect history data and physical examination findings. No single laboratory test has greater diagnostic efficacy (23). Hypoglycemia, hypothyroidism, and anemia can cause syncope. Diabetes mellitus and Addison disease (primary adrenal insufficiency) may cause syncope through volume depletion. If any of these entities is suspected, appropriate laboratory workup should be performed. Bezold Jarish phenomenon is accentuated if the child is dehydrated, as may occur following exercise, excessive sweating, or prolonged restriction of fluid intake. Sideropenia was found in three children without other pathologic findings.

The 2007 American College of Emergency Physicians (ACEP) Clinical Policy on Syncope lists history and physical examination and 12-lead ECG as their only current level A recommendations (23). Taking into account these and other guidelines (23, 24), ECG as an additional test was required and performed in all our patients with syncope irrespective of their normal physical examination.

While ECG is always indicated in the assessment of syncope in children, according to some authors, echocardiography is indicated mainly in patients with abnormal ECG findings, abnormal physical examination findings, or other features suggestive of structural heart disease (20). Specific features to assess include coronary anatomy, right and left ventricular size and function, free wall and septal thickness, left ventricular outflow tract obstruction, presence of cardiac tumors, and pulmonary artery pressure. As a tertiary diagnostic center, we performed

ECHO in 37% of our children and it was normal in all cases.

Holter monitoring is indicated in pediatric patients with recurrent syncope, although the yield of true pathology is probably about 10% (25). The specific indications for and utility of exercise testing in pediatric syncope are not identified. Patients with events that appear to be related to stress or exercise should undergo an exercise evaluation if the patient is capable.

Tilt table testing is a useful procedure for patients with undiagnosed syncope if the diagnosis has not yet been made based on a typical history and compatible physical findings (26, 27).

Typically, the patient is immobilized on a tilting bed, which is then brought to a 70° upright position for approximately 30 minutes while heart rate (ECG) and blood pressure are monitored (28). Following this, in some institutions, the patient may undergo additional tilt protocol while challenged with isoproterenol or isosorbide, decreasing the rate of false-negative results and increasing the rate of false-positive results of tilt table testing (29, 30).

The relative autonomic responses are helpful in determining whether the faint is primarily hypotensive (vasodepressor), bradycardic (cardioinhibitory), or mixed.

Our two patients performed tilt table test, both with positive results revealing vasodepressor syncope.

Two children that presented with syncope had the definitive diagnosis of epilepsy due to repeated seizures and EEG discharges. Secondary seizures are not uncommon and are typically generalized. Following such a secondary seizure, a brief postictal phase may occur. One should always bear in mind differential diagnosis towards epilepsy.

The cause of syncope was unclassified in only 5.90% of our patients. In order to reveal the cause of syncope, the circumstances associated with loss of consciousness are important in identifying the underlying cause. A detailed history of syncope allows for differentiation between neurocardiogenic and other causes of syncope.

In conclusion, this study confirmed neurocardiogenic syncope as the most frequent type of syncope in children and stressed the need for detailed history and physical examination in every patient presenting with syncope as a clue for further evaluation of syncope and its causes.

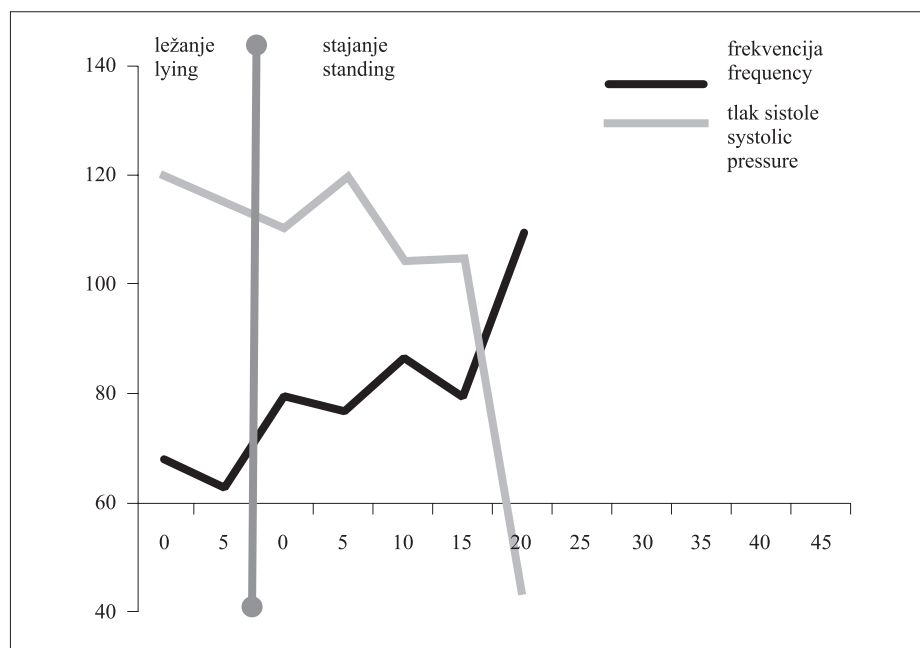


Figure 5. Tilt table test in a 17-year-old girl with syncope: after 20 minutes of orthostasis, she had clinically visible presyncope with systolic pressure drop to 40 mm Hg and tachycardia of 110/min; no asystolic pauses. Slika 5. Tilt table test u 17-godišnje djevojčice sa sinkopom: nakon 20 minuta ortostaze dobila je klinički vidljivi presinkopu s padom sistoličkog tlaka do 40 mmHg i tahikardijom do 110/min, bez asistoličkih pauza.

#### Study limitations

Some important limitations of our study must be acknowledged. First, it was a retrospective study performed at a single tertiary referral center. Furthermore, it only included patients admitted to Neuro-pediatric Unit for syncope, thus there were only 68 patients over a 2-year period. Data on those that were discharged from Emergency Department or left against medical advice were not included in analysis.

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## S a ž e t a k

### ETIOLOGIJA SINKOPA U DJECE - KOLIKO ČESTO IH TREBAMO SMATRATI NEUROGENIMA?

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*Najčešći paroksizmalni neepileptički događaji u djece su sinkope – iznenadni i privremeni gubitak svijesti, izazvan podražajima, praćen gubitkom posturalnog tonusa i s kompletnim oporavkom unutar nekoliko sekundi ili minuta. Cilj ovog istraživanja bio je utvrditi uzroke, provokacijske čimbenike, dijagnostičke procedure i klasifikaciju sinkopa u djece i adolescenata. Proveli smo retrospektivnu analizu podataka o bolesnicima koji su primljeni zbog sinkope na naš Neuropedijatrijski odsjek u 2-godišnjem razdoblju (siječanj 2005.- prosinac 2006.). Od 326-ero djece s neparoksizmalnim događajima izdvojili smo njih 68-ero s dijagnozom sinkope. Prosječna dob djece (70% djevojčica, 30% dječaka) bila je 13.67 godina. Oko 70% djece primljeno je hitno. Dvije ili više sinkopa imalo je 49% djece. Laboratorijske, neurološke i kardiološke pretrage obavljene su, ovisno o povijesti bolesti i fizikalnom pregledu. Uzroci sinkopa su bili vazovagalni, situacijski, ortostatska hipotenzija, spazam desne vertebralne arterije, psihogeni uzrok, kanal vertebralne arterije, epilepsija. Samo 5.9% sinkopa nismo uspjeli klasificirati. Najčešća sinkopa u hospitalizirane djece bila je neurokardiogena. Dijagnozu smo uglavnom postavili na temelju povijesti bolesti i fizikalnog pregleda. EEG i daljnje praćenje su potvrdili dijagnozu epilepsije u dvoje djece.*

Deskriptori: SINKOPA – klasifikacija, dijagnoza; DIJETE; SINKOPA, VAZOVAGALNA

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