Low iron storage in children with tilt positive neurally mediated syncope

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Original article

Background: **The mechanisms under neurally mediated syncope (NMS) are not fully understood. This study aimed to assess the level of storage iron in children with different hemodynamic patterns in head-up tilt test.**

Methods: **Altogether 210 children (11.31±2.49 years) with syncope or pre-syncope treated between May 2008 and September 2010 were studied prospectively. Following history taking and physical examination, their levels of hemoglobin (Hb), hematocrit (Hct) and serum ferritin were measured.**

Results: **In the 210 children, 162 (77.1%) had NMS and 48 (22.9%) had syncope due to other causes. In the 162 children with NMS, 98 children were subjected to positive tilt test. The level of serum ferritin was significantly lower in the 98 children with NMS (P<0.001). The comparison of levels of Hb, Hct and mean cell volume (MCV) displayed no significant difference between the two groups. Reduced iron storage (serum ferritin <25 ng/mL) was found to be more prevalent in children with NMS (63% *vs.* 20%, P<0.001). Prevalence of iron deficiency was also significantly higher in children with NMS than in children with syncope due to other causes (27% *vs.* 6%, P=0.003).**

Conclusions: **In head-up tilt test positive children with NMS, the level of serum ferritin should be evaluated. Low storage iron may be one of the underlying mechanisms of NMS.**

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Key words: **head-up tilt table test; neutrally mediated syncope; serum ferritin**

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Introduction

Syncope remains one of the most widespread, still annoying, sign-complexes in children, which are characterized by abrupt loss of consciousness and postural tone with complete recovery of symptoms. Syncope is a common problem in children and adolescents, with 15% to 25% of them experiencing at least one syncopal episode in early adulthood.[1] The most common form of syncope in children is neurally mediated syncope (NMS), frequently denoted as the simple faint, which comprises nearly 75% or more of patients.[2-4] Diagnosis of NMS is established by history, frequently verified by tilt testing.[5] The presentation of syncope possibly will be dramatic, and direct physicians to suspect a malignant cardiac situation.

Thus studies proposed that patients with NMS have a high prevalence of orthostatic intolerance and chronic fatigue syndrome.[6,7] There is also evidence from studies in adults that iron deficiency anemia may have a role in the pathogenesis of chronic fatigue.[8] Besides, investigations in patients with orthostatic hypotension have demonstrated a beneficial effect following the use of erythropoietin, commonly given with iron supplementation.[9] Moreover, there are reports suggesting that breath-holding spell, a brief period of loss of consciousness in infants and young children, shares similar pathophysiological mechanisms with NMS.[10] It has been shown that iron has a therapeutic effect on children with breath holding spell, even if they are non-anemic.[11]

We hypothesized that low iron may have a role in the pathogenesis of NMS. Therefore, we assessed the complete blood count and iron parameters in children, who had a history of recurrent syncope attacks.

Methods

Study population

The study was approved by the ethical committee of Izmir Behcet Uz Children's Hospital, and followed the *Declaration of Helsinki*. Informed consents were obtained from parents of each child. Between May

2008 and August 2010, 210 children (aged 11.31±2.49 years) with syncope or pre-syncope were prospectively evaluated for eligibility to participate in the study. Syncope was defined as loss of consciousness or loss of posture. Presence of any premonitory signs of an imminent syncope was described as pre-syncope. Patients with structural heart disease, congenital long QT syndrome, Brugada syndrome, chronic illnesses (diabetes mellitus, renal or liver disease), acute systemic illness or those on medication recognized to alter heart rate or to cause orthostatic hypotension were excluded. The inclusion criteria were as follows: (1) age younger than 18 years; (2) history of NMS; (3) less than 6 months between index episode of syncope, pre-syncope and first assessment; and (4) no history of infection at the time of blood sampling. Physical examination, 12-lead electrocardiography and transthoracic echocardiography were normal in all subjects who were recruited in the study.

Head-up test protocol

All children were tested in the morning after fasting for 8 hours. Studies were carried out in silent, dimly lit room at a comfortable ambient temperature (20°C-24°C). Heart rate was monitored continuously, and blood pressure was recorded every 2 minutes using an automatic sphygmomanometer. The children were then kept in a supine position for 10 minutes. Subsequently, they were tilted to a head-up position at 85° for 20 minutes. Previous reports showed that this protocol was associated with optimal and adequate sensitivity rates.[12,13] Positive response was defined as the occurrence of syncope or pre-syncope during the head-up tilt test, accompanied by at least one of the following signs:[14] (1) bradycardia, characterized by heart rate <75 bpm in children of 4 to 6 years old, heart rate <65 bpm in children of 7 to 8 years old, heart rate <60 bpm in children of more than 8 years old, sinus arrest, degree II or greater atrioventricular block and asystole for 3 seconds; (2) hypotension defined as ≤80 mmHg in systolic blood pressure or drop of >15 mmHg or/and diastolic blood pressure <50 mmHg; and (3) junctional rhythm together with escaped rhythm and accelerated idioventricular rhythm. Cardioinhibitory response was defined as an abrupt decrease in heart rate. Vasodepressor response was defined as a decrease in blood pressure. The mixed pattern was characterized by a decrease in both heart rate and blood pressure.[15] Postural orthostatic tachycardia syndrome (POTS) was diagnosed on the basis of a heart rate increase >30 bpm or the maximum heart rate >120 bpm in the absence of profound hypotension but reproducing light headedness, fatigue, pre-syncope and dizziness.[16]

Study design

The history of first event was taken from the child, the parents, and other witnesses if possible. Afterwards, all the children were re-evaluated, and symptoms were ordered into two sets. Children who fit the inclusion criteria were assigned to the NMS group. The criteria applied to classify the attack of loss of consciousness as revealing sign of NMS have been described previously in detail.[17,18] The inclusion criteria for NMS were as follows: a short period of attack, syncope characterized by the existence of triggering factors (e.g., strong fear, pain, medical procedure, heat), syncope with POTS or autonomic dysfunction. We excluded children who had negative tilt test. Children, who did not meet any condition of the inclusion criteria for NMS, formed the other syncope group. The other syncope group comprised children with uncertain, metabolic and neurological causes of syncope. The children with tilt positive were divided into two groups according to the tilt response pattern as POTS group and vasovagal syncope (VVS) group.

Analytical methods

Blood samples were obtained for analysis of serum ferritin, hemoglobin (Hb), hematocrit (Hct) and mean cell volume (MCV). The samples were collected after an 8-hour fasting in the morning. Iron deficiency was defined with a ferritin level of less than 15 ng/mL.[19] Low iron level was considered if it was lower than 25 ng/mL.[20,21] Iron deficiency anemia was defined as iron deficiency plus low hemoglobin values.[22]

Statistical analysis

The results of descriptive analysis were expressed as mean ± SD for numerical variables. The normality of distribution was examined by the Kolmogorov-Smirnov test. Only one parameter, serum ferritin, was not normally distributed. The mean values of normally distributed variables were compared between the groups using Student's *t* test; if not normally distributed using the Mann-Whitney *U* test. The Kruskal-Wallis test was used to determine statistical significance between continuous variables. If the overall *P* value was significant, the Mann-Whitney *U* test was conducted to evaluate the differences among the groups. The Chi-square test was performed for each categorical variable.

Results

The demographic and clinical characteristics of our study are shown in Table 1. Among the 210 children with syncope, 162 (77.1%) had NMS and 48 (22.9 %) had syncope due to other causes. In the 162 children

with NMS, 98 had a positive tilt test. No significant difference was found in mean age and sex distribution between the two groups (P=0.545 and P=0.409, respectively). The prevalence of palm sweat was higher in the NMS group than in the other causes group (P<0.001). However, there was no significant difference in headache and pale frequency between the two groups (P=0.26 and P=0.26, respectively).

During the head-up tilt table test, vasodepressor response was seen in 16 of the 98 children in the NMS group, cardioinhibitory response in 13, mixed pattern response in 21, and POTS pattern in 48.

Clinical and laboratory studies in the 48 children with syncope other than NMS revealed that 22 children had neurological problems (epilepsy, hyperventilation syndrome, and head injury), 7 had atypical syncope (conversion), and 2 had cardiac problems (aortic stenosis, arrhythmia). No definite cause was found in 17 patients. Hematological parameters and ferritin levels in both groups are shown in Table 2. The ferritin level was found to be significantly lower in children in the NMS group than in those in the other causes group (P<0.001). On the other hand, the comparison of Hb, Hct and MCV levels showed no significant difference between the two groups. Reduced iron storage (serum ferritin <25 ng/mL), pointing to either probable inadequate or almost totally depleted iron stores, was found to be more prevalent among children with NMS (63% *vs.* 20%, P<0.001). Iron deficiency was observed more often in children with NMS than those with syncope due to other causes (27% *vs.* 6%, P=0.003). Iron deficiency was observed in 27 of the 98 children in the NMS group and in 48 children in the other causes group. In the 98 children with NMS, 50 (34.2%) demonstrated VVS pattern and 48 (32.9%) POTS pattern. When the Kruskal-Wallis test was used to evaluate the significance of differences in the levels of ferritin among the above-mentioned groups, it was demonstrated that children with vasovagal syncope patterns and POTS patterns had significantly lower serum ferritin levels than the other causes group (24.50±14.37 ng/mL, 24.20±17.24 ng/mL, 39.25±18.45 ng/mL, respectively, P<0.001, Fig.). Furthermore, there was no significant difference in iron and hematological indices between children with vasovagal syncope and those with POTS (Table 3).

Table 1. Demographic and clinical characteristics of subjects

Characteristics	NMS group	Other syncope group	*P* value
Number of subjects	98	48	
Age (mean ± SD) (y)	11.46±2.28	11.19±2.97	NS*
Sex (male/female)	48/50	21/27	NS†
Symptoms			
Headache (*n*, %)	59, 60%	31, 65%	NS†
Pale (*n*, %)	69, 70%	29, 60%	NS†
Palm sweat (*n*, %)	55, 56%	12, 25%	<0.001†

P values were calculated by *t* test. †: *P* values were calculated by chi-square analysis. NMS: neurally mediated syncope; NS: not significant.

Table 2. Ferritin and hematological indices in children with neurally mediated syncope (NMS) against the other syncope group

Characteristics	NMS group (*n*=98)	Other syncope group (*n*=48)	*P* value
Serum ferritin (ng/mL)	24.36±15.76	39.25±18.45	<0.001*
Hemoglobin (g/dL)	12.37±0.65	12.75±0.71	NS†
Hematocrit (%)	36.35±2.19	37.51±2.26	NS†
Mean cell volume (fL)	81.53±4.96	83.48±2.48	NS†
Patients with iron deficiency anemia, *n* (%)	12 (12)	4 (9)	NS‡

Variables are expressed as mean ± SD. *: *P* values were calculated by Mann-Whitney *U* test; †: *P* values were calculated by *t* test; ‡: *P* values were calculated by chi-square analysis. NS: not significant.

Table 3. Iron and hematological indices in children with VVS and POTS

Characteristics	VVS (*n*=50)	POTS (*n*=48)	*P* value
Serum ferritin (ng/mL)	24.50±14.37	24.20±17.24	NS*
Hemoglobin (g/dL)	12.41±0.67	12.34±0.83	NS†
Hematocrit (%)	36.53±3.26	36.17±2.61	NS†
Mean cell volume (fL)	81.72±5.03	81.35±3.47	NS†
Patients with reduced iron storage, *n* (%)	17 (34%)	19 (61%)	NS‡
Patients with iron deficiency, *n* (%)	16 (32%)	11 (23%)	NS‡

Variables are expressed as mean ± SD. *: *P* values were calculated by Mann-Whitney *U* test; †: *P* values were calculated by *t* test; ‡: *P* values were calculated by chi-square analysis. VVS: vasovagal syncope; POTS: postural orthostatic tachycardia syndrome; NS: not significant.

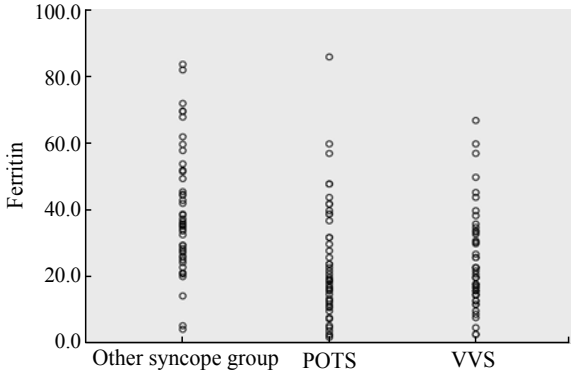

Fig. Ferritin scatter plot (mean values of ferritin as ng/mL) for children with other syncope, POTS and VVS. POTS: postural orthostatic tachycardia syndrome; VVS: vasovagal syncope.

Discussion

We investigated the relationship between serum ferritin and NMS as well as the relationship between ferritin and types of NMS. We also investigated hemoglobin, hematocrit and MCV in children with NMS. To our knowledge, this is the first study to evaluate

iron deficiency in different types of NMS which is confirmed by tilt table test although some aspects have been covered previously.[23] The determination of serum ferritin as a simple laboratory method for assessing the amount of the body iron store was performed in the 1970s.[24] Although the level of serum ferritin is a distinctive marker for the initial stage of iron deficiency, the limitation of serum ferritin is the boost in iron levels that occurs independently in children with inflammation, malignancy or liver disease.[25] Further commonly used laboratory tests such as serum iron, total iron binding capacity, mean corpuscular volume and transferrin saturation are of less diagnostic significance over ferritin.[26] Decreased iron storage or serum ferritin <25 ng/mL was 2.5 times more prevalent in 56.1% of children with NMS than in healthy children. However, no difference was observed in prevalence of low iron storage among subsets of NMS. Depleted iron store and reduced transport iron (as measured by transferrin saturation) occur in children with iron deficient erythropoiesis, which is the second stage of iron deficiency.[21] Jarjour and Jarjour[23] found that low transferrin saturation as an indicator for iron deficient erythropoiesis was present in 23% of children with NMS. The last stage of iron deficiency is anemia. According to Hallberg,[26] in patients with nutritional deficiency, in whom anemia is usually insignificant, a great number of children with iron deficiency would not be recognized via measurements of hemoglobin, because of the overlapping of normal and pathological findings. In the present study, no significant differences in hemoglobin and hematocrit were found between children with NMS and those with syncope due to other causes. However, anemia was more prevalent in the NMS group than in the other causes group.

The mechanisms underlying syncopal episodes have been the topic of clinical-investigative interest during the last decade. There are various reports suggesting that sympathoneural and adrenomedullary hormonal systems play crucial roles in several expression of cardiovascular stress response.[27] Epinephrine and norepinephrine may circulate for 1 to 3 minutes to preserve a somewhat prolonged symphathoexcitatory effect.[28] A clinical study demonstrated that there is a common dissociation between sympathoneural and adrenomedullary catecholamine release during the syncope episode.[29] Kikushima et al[30] found that epinephrine surge possibly will activate NMS. Evidence from several animal studies suggested that epinephrine can increase the activity of ventricular mechanoreceptors and provoke the Bezold-Jarisch reflex through dynamic contraction.[31,32] Moreover, high plasma norepinephrine levels are found in children with postural orthostatic tachycardia syndrome.[33] Some reports suggested that iron deficiency may be linked to alterations in catecholamine metabolism. This finding is supported by the evidence that monoamine oxidase activity is reduced in iron-deficiency rats.[34] *In vivo* studies also suggested that platelets of patients with iron deficiency include decreased monoamine oxidase activity.[35] It is known that catecholamines such as epinephrine and norepinephrine are metabolized by monoamine oxidase. Urinary norepinephrine was found to be higher in children with iron deficiency than in normal children and the high level of urinary norepinephrine was reversed after one week of iron therapy.[36] We found that the prevalence of palm sweat was greater in children with NMS than in those with syncope due to other causes. It was found that sympathetic nervous hyperactivity may lead to palmar hyperhidrosis.[37] The result of our study confirmed the role of the sympathetic nervous system in the pathogenesis of NMS.

Since the early 1980s, studies have focused on the association of iron and cardiovascular diseases.[38-42] It was found that iron deficiency can lead to ventricular hypertrophy in developing rats.[38,39,41] Although the exact pathogenesis of ventricular hypertrophy in iron deficiency is not clear, the underlying mechanisms are supposed to be changes of blood volume, chronic elevation of sympathetic nervous activity, and alterations of alpha and beta receptor expressions in the heart.[43,44] Moreover, changes in distensibility of the abdominal aorta were observed in rats.[41] Turner et al[41] found that iron deficiency hypertrophic hearts demonstrated altered cardiovascular response to intravenous epinephrine, and the abdominal aorta of iron deficiency rats displayed significantly increased distensibility. Reduced peripheral vascular resistance in anemic patients is another theory describing the association of iron deficiency and NMS.[45] Furuland et al[45] reported that normalization of hemoglobin after erythropoietin therapy elevated blood viscosity and peripheral vascular resistance in predialysis patients. In the present study, although hemoglobin levels were slightly lower in children with NMS, they were not significantly different from those in children with syncope due to other causes. We also did not find any significant difference in the prevalence of iron deficiency anemia between children with NMS and those with syncope due to other causes. Clinical studies suggested that decreased erythrocyte mass may play a role in the pathogenesis of patients with orthostatic hypotension and chronic fatigue.[9,46] Erythropoietin therapy might be effective to such patients.[46] Similar findings have also been observed in patients with POTS. Raj et al[47] reported that patients with POTS have a deficit in red blood cell volume. In the mentioned studies, however, hemoglobin levels and iron indices

were not determined.

In this study, limitations include the possible bias caused by excluding hematological parameters of patients who had negative tilt test and lack of data on iron indices and hematological parameters in Turkish children and adolescents. Therefore, reference values reported by others[20,22] were used. In conclusion, the present study shows that low serum ferritin may cause NMS. Serum ferritin should be measured in children with NMS. Further investigations for a large group of patients are needed to elucidate the role of low iron storage in the pathogenesis of NMS.

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Ethical approval: Our study was conducted according to the proper standards and ethics, and approved by the Izmir Dr Behcet Uz Children's Hospital Ethical Committee.

Competing interest: None to declare.

Contributors: Guven B was the responsible investigator. Oner T contributed to collection of data and manuscript editing. Tavli V was the head of the study. Yilmazer MM contributed to collection of data. Demirpence S contributed to data analysis. Mese T contributed to collection of data and data analysis.

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