Low Iron Storage in Children and Adolescents with Neurally Mediated Syncope

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Objective To investigate whether neurally mediated syncope (NMS) is associated with low iron storage or serum ferritin (SF).

Study design 206 children evaluated between 2000 and 2004 for probable syncope at a tertiary care Pediatric Neurology Clinic were included in a retrospective study. Serum ferritin (SF), iron, total iron binding capacity, and hemoglobin were measured prospectively after initial history taking and physical examination, along with other diagnostic testing. We defined iron deficiency (ID) as SF <12 μg/L, and low iron storage as SF ≤25 μg/L.

Results Among 106 included patients with syncope, 71 had NMS and 35 had other causes of syncope. Patients with NMS, when compared with those with other causes of syncope, had a higher prevalence of low iron storage (57% vs 17%, $P < .001$) and lower mean values of SF (27 vs 46 μg/L, $P < .001$), transferrin saturation (23 vs 31 %, $P < .01$), and hemoglobin (13.3 vs 14 g/dL, $P < .05$). Only patients with NMS had ID (15%), anemia (11%), or ID with anemia (7%).

Conclusions Low iron storage or serum ferritin is associated with NMS and is a potentially pathophysiologic factor in NMS. *(J Pediatr 2008;153:40-4)*

Syncope is a sudden, brief, self-limited, transient loss of consciousness (TLOC), usually leading to falling, with complete recovery of consciousness, which occurs as the result of global cerebral hypoperfusion, which is most often due to systemic hypotension.[1] These clinical features of TLOC, combined with the results of physical examination, help distinguish syncope from other causes of TLOC, such as an epileptic seizure, concussion, intoxication, or a conversion disorder, in the majority of pediatric patients.[1-3]

Syncope is a common problem in children and adolescents, experienced by up to 20% of them before the age of 15 years.[3] The most common type of syncope in children and adolescents is neurally mediated syncope (NMS), often referred to as the simple faint, which accounts for 75% or more of patients.[3-7] The diagnosis of NMS is based on the clinical history in most patients.[1-3] Other causes of syncope include cardiogenic syncope, acute hypovolemia, hyperventilation, and, rarely, vertebral-basilar transient ischemic attacks, in which syncope is associated with focal neurological deficits.[1,2]

To date, diagnostic tests in pediatric and adult-onset NMS have had a very low yield for a treatable etiology.[4,8-10] Patients with NMS have a high prevalence of chronic fatigue[11] and orthostatic intolerance.[12,13] Studies point to a potential role for iron deficiency (ID) without anemia in the pathogenesis of chronic fatigue.[14,15] In fact, an improvement of unexplained chronic fatigue after iron supplementation was reported in nonanemic women in one study,[14] and only nonanemic women with serum ferritin (SF) ≤50 μg/L improved in another study.[15] Moreover, studies in patients with orthostatic hypotension have shown a therapeutic benefit using recombinant erythropoietin, usually given with iron supplementation.[16,17] Furthermore, a therapeutic trial of iron has also shown benefits in nonanemic children with breath-holding spells, which is a form of NMS in early childhood.[18-20]

Based on these various reports, we evaluated complete blood count and iron indices in patients attending our clinic for probable or definite syncope. We hypothesized that children and adolescents with NMS, like some younger patients with breath-holding spells, have low iron storage or ID, without or with mild anemia.

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Hb	Hemoglobin	POTS	Postural orthostatic tachycardia syndrome
Hct	Hematocrit	SF	Serum ferritin
ID	Iron deficiency	TIBC	Total iron-binding capacity
NMS	Neurally mediated syncope	TLOC	Transient loss of consciousness
OH	Orthostatic hypotension		

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METHODS

We undertook a retrospective study of patients who presented to the Pediatric and Adolescent Neurology Clinic at Allegheny General Hospital, a tertiary care center in Pittsburgh, Pennsylvania, for an evaluation of probable syncope between 2000 and 2004. Patients were either referred to the clinic by primary care or emergency medicine physicians or were established clinic patients who developed new complaints of probable syncope. The patients were identified using ICD-9 (International Classification of Diseases-9th Revision) code 780.2 in a computerized data file. This code was used to denote a diagnosis of syncope, near-syncope, or probable syncope after the evaluation of patients by the primary investigator, using a clinical interview of each patient and parent(s) or other caregivers, and complete physical and neurological examinations. Patients who reported symptoms on standing, such as lightheadedness, had a standing test in which the pulse and blood pressure were measured manually and recorded in a standardized fashion after patient had rested in a supine position for at least 5 minutes and repeated after 3 minutes of standing. The primary investigator reviewed the medical records systematically for description of probable syncopal episodes, interval between last episode and neurological evaluation, and history of chronic or acute systemic illness or infection.

Inclusion criteria were as follows: (1) documented sudden, brief, self-limited, TLOC, with loss of posture and complete recovery of consciousness, in which syncope from cerebral hypoperfusion was a definite or likely diagnosis at the end of initial clinical evaluation; (2) age younger than 19 years; and (3) interval of less than 6 months between recent syncope and the initial evaluation. Exclusion criteria were as follows: (1) history of infection at time of blood testing; (2) the cause of TLOC at time of initial evaluation was not determined as syncope but an epileptic seizure, a concussion, or another disorder; (3) near-syncope with symptoms of impending faint but no TLOC; (4) orthostatic hypotension (OH) secondary to medications; (5) chronic illness, such as renal failure, liver disease, or diabetes mellitus; (6) acute systemic illness; and (6) inadequate historical data to ascertain TLOC and diagnosis of likely syncope.

Data from the medical records of included study patients were summarized on structured forms for each patient, including demographic data, characteristics of TLOC episode (such as warning symptoms, precipitating situations, body position, and orthostatic change at the time of TLOC), history of recurrent headaches, symptoms of orthostatic intolerance, such as dizziness (lightheadedness), pallor, blurred vision, palpitations, tremors, nausea, sleep impairment, and chronic fatigue for more than past 3 months unexplained by temporary or permanent medical or psychiatric conditions, medications at time of TLOC, results of diagnostic testing, such as blood tests, electrocardiograms, echocardiograms, electroencephalograms, computerized tomography or magnetic resonance imaging of the brain, and head-up tilt tests, and data from clinical follow up evaluations.

We defined orthostatic intolerance as all forms of illness or symptoms while standing or on standing up that are relieved by recumbence. We defined postural orthostatic tachycardia syndrome (POTS) as a rise of 30 or more beats/min in heart rate or a heart rate of >120/min after 3 minutes of standing and a history of 2 or more symptoms of orthostatic intolerance for 3 or more months' duration.[7] Chronic OH was defined as a reduction of systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg after 3 minutes of standing,[21] in addition to a history of 2 or more symptoms of orthostatic intolerance of 3 or more months' duration.

Patients meeting the study's inclusion criteria were assigned to an NMS group according to the following criteria: (1) syncope with recognized clinical characteristics of sudden TLOC after warning symptoms while standing or after sudden standing, not during exercise, in certain circumstances such as strong fear or heat or crowded rooms, with spontaneous recovery of consciousness and awareness in <2 minutes,[1,22,23] or (2) syncope with POTS or chronic OH, and (3) no cause of syncope other than NMS on further neurological or cardiac diagnostic testing and clinical follow-up evaluations. Patients with a diagnosis of syncope, based on their initial clinical evaluation, who did not meet any of the 3 criteria for NMS, formed the other syncope group and consisted of patients with cardiac, neurological, metabolic, or uncertain cause of syncope.

Laboratory tests of iron status included SF, iron, total iron-binding capacity (TIBC), hemoglobin (Hb), hematocrit (Hct), and mean cell volume (MCV). We calculated transferrin saturation by dividing serum iron by the TIBC and multiplying by 100 to express the results as a percentage. These tests were obtained in the morning, after an overnight fast, at the time of the initial neurological evaluation for syncope. We defined ID as SF values <12 μg/L, low iron storage as SF values ≤25 μg/L, and low transferrin saturation as values <16%.[24,25] We defined ID anemia as ID and low Hb values for age and sex, which were derived from the study of Looker et al.[26]

Continuous variables of iron and hematological indices were compared between NMS and other syncope groups, using an independent-samples t test and analysis of covariance to control for age and sex. The frequency of low iron storage was compared using logistic regression with calculation of odds ratios (OR) and confidence intervals (CI) while controlling for age and sex as potential confounding factors. Differences between the ages of patients in NMS and other syncope groups were evaluated using an independent-samples t test, whereas sex differences and the prevalence of comorbid conditions were evaluated using Pearson χ^2. Institutional review board approval was granted for this study.

RESULTS

Of a total 206 patients younger than 19 years of age who were evaluated for probable syncope, 106 met the study's inclusion criteria. The remaining 100 patients were excluded