Original Article

Iron Insufficiency and Hypovitaminosis D in Adolescents with Chronic Fatigue and Orthostatic Intolerance

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Objectives: More than 10% of adolescents suffer from severe fatigue and/or orthostatic intolerance. Adult studies show correlations between iron insufficiency and fatigue as well as between hypovitaminosis D and non-specific pain. We sought to determine whether there were correlations between nutritional factors (iron status, and serum vitamin D levels) and chronic ill health.

Methods: We reviewed records of 188 adolescents with symptoms of fatigue and/or orthostatic intolerance and who underwent autonomic reflex screening.

Results: Of the 188 patients, 130 patients (69%) had excessive postural tachycardia (PT) with a heart rate (HR) change of ≥30 bpm. 62 patients (47%, n = 131) had iron insufficiency with low iron stores, and 29 patients (22%, n = 131) were iron deficient. HR change did not correlate to ferritin level ($P = 0.15$). 21 patients (22%, n = 95) had hypovitaminosis D (25-hydroxyvitamin D ≤20 ng/mL). There was a significant association with hypovitaminosis D and orthostatic intolerance ($P = 0.024$).

Conclusion: In patients presenting with chronic fatigue and/or orthostatic intolerance, low ferritin levels and hypovitaminosis D are common, especially in patients with PT.

Key Words: adolescents, hypovitaminosis D, low iron storage, orthostatic intolerance

Chronic fatigue is common among adolescents with 11–17% reporting severe fatigue.[1] Orthostatic intolerance is often identified in fatigued patients and includes excessive palpitations, nausea, lightheadedness, headache, sweating, occasional visual changes, syncope, or presyncope.[2] Chronic orthostatic intolerance is defined as the development of these symptoms related to an upright posture.[3] Symptoms are relieved by recumbence. Chronic orthostatic intolerance commonly manifests in adolescence as postural orthostatic tachycardia syndrome, a clinical syndrome characterized by symptoms of orthostatic intolerance associated with a heart rate increment exceeding 30 beats per minute on head-up tilt (HUT).[2] However, the proportion of adolescents with chronic orthostatic intolerance who have sufficient heart rate increment on head-up tilt to meet criteria for postural orthostatic tachycardia syndrome remains unknown. The majority of research on adolescent autonomic dysfunction, and specifically adolescent orthostatic intolerance, has focused on patients with postural orthostatic tachycardia syndrome.

While the exact pathogenesis of chronic fatigue and orthostatic intolerance is unknown, adult studies have found correlations between iron deficiency and fatigue[4] as well as correlations between hypovitaminosis D and non-specific musculoskeletal pain.[5] It has recently been reported that neurally mediated syncope in children is associated with iron insufficiency.[6] We hypothesized that nutritional factors, including iron status and serum vitamin D levels, would be

Key Points

- Chronic fatigue is common among adolescents, with 11–17% reporting severe fatigue.
- Adult studies have found correlations between iron deficiency and fatigue as well as correlations between hypovitaminosis D and non-specific musculoskeletal pain.
- Hypovitaminosis D and iron insufficiency are common in adolescents with chronic fatigue and/or orthostatic intolerance and appear to be more prevalent than in normal populations.

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associated with chronic ill health, as indicated by severity of orthostatic intolerance.

Material and Methods

We retrospectively reviewed the medical records of all adolescent patients (age 13 to 18) who had been seen in a pediatric diagnostic referral clinic with a variety of symptoms potentially related to orthostatic intolerance. Patients had been evaluated at Mayo Clinic (Rochester, Minnesota) between August 2002, and July 2007. This study was approved by the Mayo Clinic Institutional Review Board.

As part of their medical evaluation in the diagnostic clinic, the patient's self-report of symptoms of orthostatic intolerance was assessed and recorded, including excessive palpitations upon standing often accompanied by fatigue, nausea, headache, and presyncope. The majority of patients underwent a standardized autonomic reflex screen including a HUT to 70 degrees, and blood pressure and heart rate responses were recorded at 1, 5, and 10 minutes. Furthermore, the results of the following tests, when available, were evaluated: serum hemoglobin; serum ferritin; serum total 25-hydroxyvitamin D; and peak oxygen uptake ($VO_{2\ max}$) on cardiopulmonary exercise testing. We defined iron deficiency as serum ferritin < 12 μg/L, and low iron storage as serum ferritin ≤ 25 μg/L. Hypovitaminosis D was defined as 25-hydroxyvitamin D levels of ≤ 20 ng/mL. The chi-square test examined associations among categorical variables, and the Pearson correlation coefficient tested correlations among continuous variables. All tests were 2-tailed. Statistical analyses were performed using SAS 9.2 (Cary, North Carolina).

Results

In this population of chronically ill adolescents, we identified 206 patients (mean ± SD age, 15.1 ± 2.2 years; 73% female) with a mean duration of symptoms of 2.5 years. Commonly reported symptoms included dizziness upon standing (84%), fatigue (71%), headaches (63%), and nausea (54%). The mean BMI in this cohort was 21.8 ± 3.9 kg/m^2 (n = 201). A total of 56 patients (28%) were classified as overweight (BMI > 85th percentile).

Of the 206 patients, 188 (91%) underwent autonomic reflex screening, including a HUT. During HUT, the mean postural heart rate (HR) change was 36.1 ± 13.6 bpm. One hundred thirty patients (69%) had excessive postural tachycardia (PT) with an HR change of ≥ 30 bpm, and 77% of PT patients were female. Of all PT patients, only 17 (13%) patients displayed orthostatic hypotension, defined as >20 mmHg drop in systolic blood pressure over 10 minutes of HUT.

The mean serum ferritin was 31 μg/L (n = 131, SD = 39.67). A total of 62 patients (47%) had low iron stores (serum ferritin ≤ 25 μg/L) and 29 patients (22%) were iron deficient (serum ferritin < 12 μg/L). Of the patients with PT, 56% had low iron stores and 23% of these patients were iron deficient. In contrast, of the patients without PT, 28% had low iron stores and 20% of these patients were iron deficient (Fig. 1). Furthermore, there was no statistically significant correlation between postural heart rate change and low ferritin ($P = 0.15$).

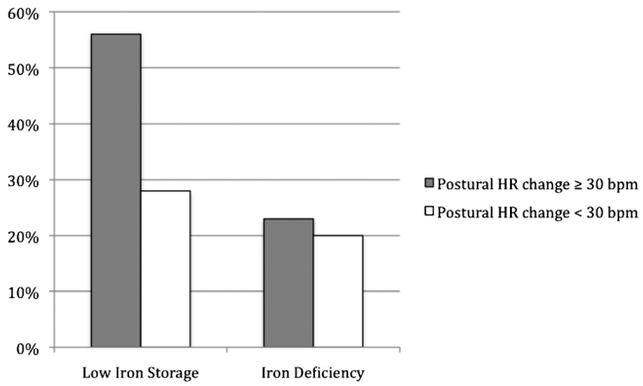

Fig. 1 Prevalence of low ferritin levels in patients with and without postural heart rate changes 30 bpm or greater.

The mean vitamin D level was 29 ± 12 ng/mL (n = 95). 21 patients (22%) had hypovitaminosis D. The prevalence of hypovitaminosis D was 30% among patients with PT, compared with 10% among patients without PT. There was a statistically significant correlation between PT and the presence of hypovitaminosis D ($P = 0.024$).

Discussion

Nutritional deficiency was common in our cohort of adolescents with chronic fatigue and/or orthostatic intolerance. Approximately 50% of our subjects had iron insufficiency with low iron stores, and approximately 20% of the cohort was iron deficient. Within this clinically heterogenous population, however, serum ferritin levels did not correlate with postural HR change. This is in contradistinction to the association between low iron stores and neurally mediated syncope,[6] perhaps because most of our patients had significant comorbidities including, for many, deconditioning. It has been hypothesized that this association is the result of abnormal catecholamine metabolism.[6] One form of postural orthostatic tachycardia syndrome, classified as "hyperadrenergic," has serum norepinephrine levels >600 ng/mL.[7] We speculate that future prospective studies examining adolescents with hyperadrenergic PT might demonstrate more impairment of iron storage.

There was a significant association with hypovitaminosis D and orthostatic intolerance as evidenced by the presence of excessive postural tachycardia. To our knowledge, this is the first report of a possible association of hypovitaminosis D and PT. Although there is no clear consensus despite a significant amount of research and clinical work in this field, many experts define hypovitaminosis D as 25-hydroxyvitamin D levels of ≤ 20 ng/mL, with optimal

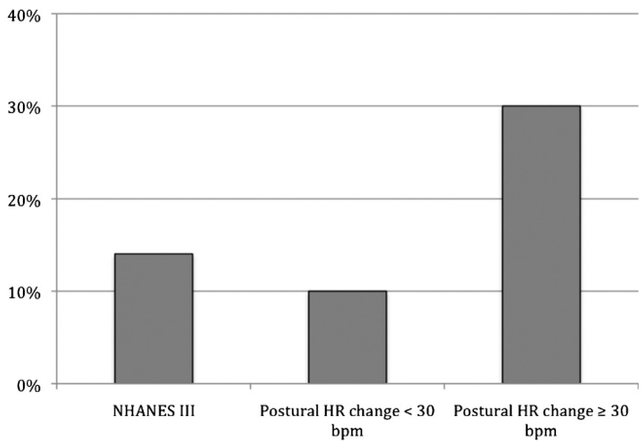

Fig. 2 Prevalence of hypovitaminosis D (defined as total hydroxyvitamin D ≤20 ng/mL) among patients with and without postural heart rate changes 30 bpm or greater compared with a normal multiracial US adolescent population.[8]

levels as being 30–60 ng/mL.[5] This study is limited by its retrospective nature and thus its lack of a matched control group. However, when we compare our patients to a nationally representative sample of patients ages 12–19 (n = 2955) our study demonstrates a marked increase in the prevalence of hypovitaminosis D from 14% in the normal adolescent population[8] to 30% in adolescent patients with PT (Fig. 2).

The mechanisms by which hypovitaminosis D relates to pain[5] and postural tachycardia are unknown and deserve further study. The national rise in adolescent and adult hypovitaminosis D, when comparing prevalence from 1988–1994 and 2000–2004, has been attributed to high BMIs, decreased milk intake, increased sunscreen use, and decreased outdoor activity.[9] Future prospective studies must elucidate if the prevalence of hypovitaminosis D we describe is a causative factor of orthostatic intolerance or if it is simply the result of factors such as decreased outdoor activity, which accompanies chronic fatigue and orthostatic intolerance. Although its role in calcium absorption and utilization has long been known, the recent discovery of the vitamin D receptor in many tissues and cells within the body has significantly broadened the understanding of the potential functions of this vitamin. These functions include gene regulation, immunomodulation, and potential effects upon the cardiovascular system (possibly by way of the alterations in parathyroid hormone levels, changed as a result of the vitamin D deficiency).[10,11]

Our study has several important limitations. Associations from this retrospective review cannot establish causal relationships. Symptoms of orthostatic intolerance were identified retrospectively from medical records rather than prospectively via a standardized questionnaire. Finally, the identified cohort, although presenting with similar symptoms, did not undergo identical testing.

Conclusion

Prospective studies will need to be designed to understand the role of iron and vitamin D in patients with orthostatic intolerance. Despite limitations, the current descriptive study should stimulate further investigation by pointing out that hypovitaminosis D and iron insufficiency are common in adolescents with chronic fatigue and/or orthostatic intolerance and appear to be more prevalent than in normal populations.

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