Pediatric Neurology 49 (2013) 274–278

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Relationship of Serum Ferritin Levels to Sleep Fragmentation and Periodic Limb Movements of Sleep on Polysomnography in Autism Spectrum Disorders

Julie Youssef DO [a], Kanwaljit Singh MD, MPH [b,c], Noelle Huntington PhD [a], Ronald Becker MD [a], Sanjeev V. Kothare MD [c,*]

[a] *Division of Developmental Medicine, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts*
[b] *Lurie Center for Autism, Massachusetts General Hospital for Children, Harvard Medical School, Boston, Massachusetts*
[c] *Division of Clinical Neurophysiology, Department of Neurology, Children's Hospital, Harvard Medical School, Boston, Massachusetts*

ABSTRACT

OBJECTIVE: Although children with autism spectrum disorders experience a range of sleep disturbances, exact mechanisms are not well-characterized. We investigated the association of serum-ferritin to sleep fragmentation and periodic limb movements of sleep using polysomnography in children with autism spectrum disorders. **METHODS:** We conducted a retrospective chart review of children with autism spectrum disorders followed from 1990 to 2010. Inclusion criteria were availability of polysomnography data and ferritin levels within 12 months of each other. The following variables on polysomnography characterized sleep fragmentation: increased arousal index, alpha intrusions, and reduced sleep efficiency. The data were compared with age- and gender-matched controls. **RESULTS:** Of 9791 children with autism spectrum disorders identified, 511 had a ferritin level, 377 had polysomnography data, and 53 had both ferritin and polysomnography data. As compared with the controls (86 ng/mL), the median ferritin level was 27 ng/mL in the study autism spectrum disorders population (53 patients) ($P < 0.01$), 27 ng/mL in autism spectrum disorder subjects with periodic limb movements of sleep (25 patients) ($P = 0.01$), and 24 ng/mL in autism spectrum disorders subjects with sleep fragmentation (21 patients) ($P = 0.02$). Within the autism spectrum disorders population, median ferritin levels were significantly lower in patients with poor sleep efficiency (7 ng/mL) versus those with normal sleep efficiency (29 ng/mL) ($P = 0.01$). The prevalence of periodic limb movements of sleep was 47% in autism spectrum disorders compared with 8% in controls ($P < 0.01$). **CONCLUSION:** Children with autism spectrum disorders had significantly lower ferritin levels compared with controls. In addition, they experience a higher prevalence of sleep fragmentation, obstructive sleep apnea, and periodic limb movements of sleep than children with ASD and no sleep complaints. Our preliminary observations, which have not been described before, need to be validated in multicenter prospective studies.

Keywords: autism, sleep, ferritin levels, iron deficiency

Pediatr Neurol 2013; 49: 274-278

Introduction

Autism spectrum disorders (ASDs) are neurodevelopmental disorders with multifaceted etiology. It is hypothesized that children with ASDs have abnormal neuronal connectivity, synaptic functioning, and neurotransmitter imbalances.[1,2] Children with ASD may be at risk for low ferritin levels and anemia because of their poor dietary intake of iron.[3] Patients with ASD are also known to be at risk of sleep disorders and dysregulation of sleep/wake cycle; up to 60% of individuals with ASD have disturbed sleep, including sleep fragmentation and frequent nighttime arousals.[4-6]

The sleep-wake cycle is at least in part controlled by the dopamine-opiate system,[7,8] in which iron is an essential cofactor.[9] Hence, iron deficiency may impair dopaminergic function and thus affect the sleep-wake cycle. Although serum iron levels may be measured directly in the blood, these levels are not a sensitive indicator of iron stores because they increase immediately upon iron supplementation. In contrast, ferritin levels usually have a direct

Article History:
Received 22 April 2013; Accepted 27 June 2013
* Communications should be addressed to: Dr. Kothare, whose present address is: Comprehensive Epilepsy Center, New York University Medical Center 223 East 34th Street, New York, NY 10016.
E-mail address: sanjeev.kothare@nyumc.org

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http://dx.doi.org/10.1016/j.pediatrneurol.2013.06.012

correlation with the body stores of iron and thus have a high specificity in the diagnosis of iron deficiency.

Periodic limb movements of sleep (PLMS) are 0.5-5.0 seconds' duration repetitive and rhythmic movement of the limbs each separated by 5-90 seconds and occurring in clusters of four or more.[10,11] There is some evidence that PLMS have been associated with iron deficiency anemia and other chronic illnesses[12]; however, the volume of pediatric literature is rather limited regarding the prevalence and correlates of PLMS in children and adolescents.[13]

Sleep fragmentation is characterized by repetitive short interruptions of sleep seen on electroencephalography[14-16] and is often manifested by nonspecific daytime somnolence or irritability.[17] It places children at risk for adverse cardiovascular, neurological, and metabolic outcomes because of underlying obstructive apnea, hypoxemia, or hypoventilation.[18] Additionally, the additive effects of sleep fragmentation could lead to profound neurocognitive deficits over time.[19]

Previous studies have examined the relationship between ferritin and sleep disturbances in children with ASDs, using subjective parental report. An 8-week open-label trial of iron supplementation was performed in children with ASD, low ferritin levels, and parent-reported sleep disturbances. Supplemental iron treatment resulted in reduction in restless sleep in 29% of the participants and increased ferritin levels.[20] Although this study suggested an association between ferritin and sleep disturbances, it is limited by its reliance on subjective parental report, which has been proven to not be an accurate predictor on polysomnography (PSG).[21]

Because sleep fragmentation could present with nonspecific behavioral changes, it is crucial to rule out sleep difficulties in patients with ASDs as well as better understand potential causes of these sleep difficulties. The primary objective of our study was to assess the relationship of serum ferritin levels in children with ASD with or without sleep fragmentation or PLMS on PSG.

Materials and Methods

This was a retrospective cross-sectional chart review of patients with ASD who were evaluated at Boston Children's Hospital between January 1, 2000, and December 31, 2010. Children younger than 21 years with an *International Classification of Diseases*-9 diagnosis of ASD who had documented complete blood count and iron studies (including ferritin levels) and a PSG within 1 year of the serum ferritin level were included in the study. In patients with multiple ferritin levels within the year, the value closest to the date of PSG was used. Data on age, gender, medication use, and comorbid medical, hematologic, neuromuscular, and psychiatric disorders were collected. An equal number of age- and sex-matched children without ASD referred for further evaluation of various sleep complaints were also included in the study.

The primary predictor of interest was serum ferritin level. The mean and standard deviation were reported and compared with the institutional norm. The primary outcome was evidence of sleep fragmentation on PSG, which was defined as an abnormality in at least one of the following parameters: arousal index (number of arousals/hour associated with electroencephalography arousal) >10/hour; alpha intrusions, at a minimal frequency of at least 1/minute, for >50% of the night on the PSG (alpha waves are normally present when someone is awake; therefore, their presence during sleep is a marker of abnormal sleep architecture and the presence of sleep fragmentation); and/or sleep efficiency (ratio of total sleep time to total time in bed) <85%. The secondary sleep outcome of interest was the presence of PLMS >5/hour (repetitive and rhythmic movement of the limbs, 0.5-5.0 seconds' duration, each separated by 5-90 seconds, occurring in clusters of four or more).

Statistical analysis

Demographic information, clinical characteristics, and sleep variables/parameters were reported using descriptive statistics. Wilcoxon test, a nonparametric test, was used to compare laboratory and PSG parameters because the study data were not normally distributed. A logistic regression was also performed to evaluate the association between serum ferritin levels and PSG parameters. Statistical analyses were performed on JMP v8.0.2 and SAS v9.3.

Results

Of the 9791 children with ASD who were seen during the study's time frame, 511 had ferritin levels, and 377 had undergone a PSG, but only 53 (37 boys, 16 girls) had both ferritin and PSG data and met all inclusion criteria. The median age of the study population was 8 years. PLMS were identified in 25 of 53 PSGs reviewed, indicating a prevalence of 47%. Major clinical diagnoses besides ASD included seizures, chromosomal/genetic anomalies, and structural airway anomalies. Anemia was a common medical problem in our study group, affecting 8% of boys and 20% of girls. Baseline characteristics and hematologic data for our study population are summarized in Table 1.

The median ferritin level of all 511 children with ASD was 35 ng/mL. Of those 511 patients, 175 had documentation of sleep complaints and their median ferritin level was slightly lower at 31 ng/mL.

The median ferritin level of the final study group (comprising 53 patients) who had a PSG was 27 ng/mL, which was significantly lower than the control population (86 ng/mL) ($P < 0.01$).

The prevalence of PLMS was 47% in ASDs, compared with 8% in controls ($P < 0.01$). Median ferritin level in ASD patients with PLMS was 27 ng/mL, which was significantly lower than controls ($P = 0.01$). However, median ferritin level in ASD patients with PLMS did not significantly differ from those without PLMS (26.8 ng/mL) ($P > 0.1$).

A marker of sleep fragmentation was observed in 42% of subjects. Children with at least one marker of sleep fragmentation had a median ferritin level of 24 ng/mL, which also was significantly lower than the control population ($P = 0.02$). Within patients with sleep fragmentation, children with poor sleep efficiency had a median serum ferritin of 7 ng/mL as compared with 29.1 ng/mL in children normal sleep efficiency ($P = 0.01$). Patients with other markers of sleep fragmentation (alpha intrusions and arousal index) did not have significantly different ferritin levels from the patients with no alpha intrusions and normal arousal index ($P > 0.1$). Finally, within patients with sleep fragmentation, trends for girls to have alpha intrusions ($P = 0.060$) and lower sleep efficiency ($P = 0.07$) were observed.

Thirty-seven percent of patients in our study had obstructive sleep apnea (OSA). However, neither the body mass index nor median ferritin level differed significantly between ASD patients with OSA and those without OSA ($P > 0.1$). Finally, simple logistic regression models showed that serum ferritin levels did not significantly predict the occurrence of abnormal PSG, PLMS, OSA, or sleep fragmentation ($P > 0.1$). Tables 2 and 3 list the statistics on ferritin levels and sex differences in PSG parameters, respectively.