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Original Article

Plasma IGF-1 levels and cognitive dysfunction in children with obstructive sleep apnea

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Abstract

Background: Pediatric OSA is associated with substantial morbidity in cognitive function. However, for any given OSA severity level, altered cognitive performance may or may not be present. Since IGF-1 is neuroprotective, we hypothesized that higher systemic IGF-1 levels may identify children at lower susceptibility for cognitive morbidity.

Methods: Consecutive habitually snoring and non-snoring children ages 5–7 years were recruited from the community, and underwent overnight polysomnography, and neurocognitive testing and a blood draw the next morning. Snoring children were divided into OSA or no OSA, and OSA children were further subdivided into those with $\geqslant 2$ abnormal cognitive subtests and into those with normal cognitive scores. Plasma levels of IGF-1 were also measured using ELISA.

Results: Among snoring children without OSA, circulating IGF-1 was 910 ± 110 pg/mL compared with 1070 ± 240 pg/mL in those with OSA ($p < 0.01$). However, IGF-1 was 540 ± 70 pg/mL in children with OSA and cognitive deficits, compared to 1370 ± 170 μg/L in children with OSA and normal cognitive scores ($p < 0.001$).

Conclusions: IGF-1 levels are higher in children with OSA, particularly in those who do not manifest neurocognitive deficits, suggesting that the magnitude of the IGF-1 response elicited by OSA may play a significant protective role against the neurocognitive dysfunction associated with OSA.

Keywords: Sleep apnea; Cognitive morbidity; Insulin growth factor-1; Snoring; Pediatric; Neuroprotection

1. Introduction

Obstructive sleep apnea (OSA) has now been recognized as a frequent condition affecting up to 3% of all pre-pubertal children [1]. The pathophysiological mechanisms involved in pediatric OSA are multifaceted, and likely include anatomical, craniofacial, and neuromuscular components [2]. More importantly, OSA has been clearly linked to several morbid consequences, and more particularly to the occurrence of somatic growth and neurobehavioral deficits and cardiovascular sequelae [3,4]. However, while a dose-dependent relationship exists between the severity of OSA and its associated morbidities, it needs to be emphasized that not all children with OSA will, for example, present neurobehavioral deficits [5], suggesting that factors other than disease severity may also play a role [5,6].

Insulin growth factor-1 (IGF-1) is a polyfunctional growth factor that operates as a classical hormone in the somatotropic axis, and also acts as a local humoral factor in all tissues, including the brain. Circulating IGF-1 is produced by the liver, its expression is

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regulated by hypoxia [7], and IGF-1 has also been shown to exert an important role in cognitive function and development, independent of somatic growth [8]. Systemic administration of IGF-1 leads to its transport across the blood brain barrier, elicits increased neuronal activity, hippocampal neurogenesis, and also confers resistance to a variety of central nervous system insults, including hypoxia [9]. Furthermore, in a recently studied large cohort of children, evidence supporting a role of IGF-1 and brain development emerged, whereby a significant positive association between serum IGF-1 levels and IQ was found [10]. Taken together, the cumulative evidence would suggest that alterations in circulating levels of IGF-1 by the presence of OSA in children, may in turn dictate the magnitude of neurobehavioral deficits associated with the latter condition.

In this study, we hypothesized that lower IGF-1 serum levels in children with OSA would be associated with more severe neurocognitive morbidity in children with OSA compared with age-, gender, and BMI-matched children with OSA of similar severity but with normal neurocognitive function.

2. Methods

2.1. Survey questionnaire

The study was approved by the University of Louisville Human Research Committee and the Jefferson County Public Schools (JCPS) Board. For the initial identification of potential participants, a previously validated questionnaire was used [11,12]. Parents of all children 5–7 years of age enrolling into the JCPS system were invited to complete the questionnaire, which in addition to demographic information and significant medical history of the child, included questions on whether the child had difficulty initiating sleep, restless sleep, enuresis, apnea, cyanosis during sleep, snoring and, if so, the severity of the snoring. The responses were graded as "never," "rarely" (once per week), "occasionally" (twice per week), "frequently" (3–4 times per week) and "almost always" (>4 times per week). Returned questionnaires were scanned into a computerized database using Microsoft Access, and both non-snoring children (responses of "never" or "rarely" on snore and "not applicable" on loudness of snore in questionnaire) as well as habitually snoring children (responses of "almost always" (>3 nights/week) or "always" on snoring frequency and "medium loud" to "loud" on loudness of snoring) were randomly selected and invited to the Sleep Medicine Research Center at Kosair Children's Hospital for an overnight polysomnographic assessment, followed next morning by a fasting blood draw and a battery of neurobehavioral tests. Children were excluded if they had any chronic medical conditions, genetic, craniofacial syndromes, or if they were obese.

2.2. Polysomnographic assessment

Children were studied for up to 12 h in a quiet, darkened room with an ambient temperature of 24 °C in the company of one of their parents. No drugs were used to induce sleep. The following parameters were measured during the overnight sleep recordings: chest and abdominal wall movement by respiratory impedance or inductance plethysmography, heart rate by ECG, air flow was triply monitored with a sidestream end-tidal capnograph which also provided breath-by-breath assessment of end-tidal carbon dioxide levels ($PETCO_2$; BCI SC-300, Menomonee Falls, WI), a nasal pressure cannula, and a oronasal thermistor. Arterial oxygen saturation (SpO_2) was assessed by pulse oximetry (Nellcor N 100; Nellcor Inc., Hayward, CA), with simultaneous recording of the pulse waveform. The bilateral electrooculogram (EOG), eight channels of electroencephalogram (EEG), chin and anterior tibial electromyograms (EMG), and analog output from a body position sensor (Braebon Medical Corporation, Ogdenburg, NY) were also monitored. All measures were digitized using a commercially available polysomnography system (Rembrandt, MedCare Diagnostics, Amsterdam). Tracheal sound was monitored with a microphone sensor (Sleepmate, Midlothian, VA) and a digital time-synchronized video recording was performed.

Sleep architecture was assessed by standard techniques [13] by two blinded scorers who were unaware of the identity and neurocognitive status of the subjects. The proportion of time spent in each sleep stage was expressed as percentage of total sleep time (%TST). Central, obstructive and mixed apneic events were counted. Obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movement for a duration of at least two breaths [14,15]. Hypopneas were defined as a decrease in oronasal flow of $\geqslant 50\%$ with a corresponding decrease in SpO_2 of $\geqslant 4\%$ and/or arousal [14]. The obstructive apnea/hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of TST. The obstructive apnea index (AI) was defined as the number of apneas per hour of TST. The diagnostic criteria for OSA included an obstructive apnea index >1/h TST, and/or an obstructive apnea–hypopnea index >2/h TST with a nadir oxygen saturation value of at least <92%. Control children were defined as non-snoring children with an obstructive AHI $\leqslant$1/h TST.

Height and weight were obtained from each child. Body mass index (BMI) was calculated and also expressed as relative BMI (relBMI), using the following formula: (BMI/BMI of the 50th percentile for age and gender) × 100, based on standardized percentile curves [16]. Obesity was defined as BMI greater than the 95th percentile for gender and age, and all children fulfilling obesity criteria were excluded from this study.