Laboratory Tests in Pediatric Sleep Medicine

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Leila Kheirandish-Gozal and David Gozal

Introduction

Sleep fulfills an essential and life-sustaining function. As such, it should not come as a surprise that when something is not well in the way we sleep, biological systems in many if not all of our organs will mount a response at the transcriptional and translational level, and as such lead to changes in the composition of body fluids in a predictable and consistent manner that can either serve as biomarkers of the disease or as biomarkers of the morbid consequences of the sleep disorder [1]. In addition, specific genetic risk factors may be associated with increased prevalence of a specific sleep disorder and may assist in determining whether a patient presenting with a constellation of symptoms and sign compatible with that disease is more likely to suffer from the disease or not.

In this chapter, we will review specific laboratory tests that may be useful when evaluating sleep conditions in children. Some of these tests are not necessarily implemented by all sleep practitioners, and as such the reader will have to use discretionary judgment regarding their utility in the clinical practice settings where they operate.

Pediatric Obstructive Sleep Apnea

Pediatric OSA is associated with an increased risk for a large number of comorbidities ranging from cognitive and behavioral deficits, endothelial dysfunction, and systemic hypertension, to metabolic perturbations, such as insulin resistance, dyslipidemias, as well as increased frequency of nocturnal enuresis, and excessive daytime sleepiness (EDS) [2–11]. Although the current definitive diagnostic tool for establishing the presence of OSA is based on the clinical presentation and more prominently on overnight polysomnography (PSG) [12], this labor intensive and costly test is only marginally predictive of any associated morbidities in patients with otherwise similar findings on the PSG. Indeed, although the prevalence of morbidities increases with the severity of OSA, there is still a very large proportion of children with even severe OSA who will not present any evidence of measurable morbidity. Exploration of ideal biomarker candidates that are reliably predictive of OSA-associated morbidities can be very useful and valuable in clinical decision making and in evaluating the response to treatment [13, 14]. Below is a short review of previously explored biomarkers aimed at the diagnosis of OSA or detection of OSA-associated morbidities. Some of these laboratory tests may also be helpful for other purposes rather than just sleep disorders, and such instances will be indicated when appropriate.

Diagnostic Tests

OSA-Associated Urinary Proteins

Proteomic approaches reveal that pediatric OSA is associated with specific and consistent alterations in urinary concentrations of specific protein clusters. Research shows Kallikrein-1, uromodulin, urocortin-3, and orosomucoid-1 have adequate accuracy to be used as an OSA diagnostic test in children when used in combination [15]. These assays have not been commercialized as of yet.

L. Kheirandish-Gozal (✉)
Department of Child Health and the Child Health Research Institute, University of Missouri, School of Medicine, Colombia, MO, USA
e-mail: gozall@missouri.edu

D. Gozal
Department of Child Health, MU Women's and Children's Hospital, Columbia, MO, USA

Children's Hospital Research Institute, University of Missouri, Columbia, MO, USA

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High Sensitivity C-Reactive Protein (hs-CRP)

Hs-CRP has been shown to increase in children with OS, and the more severe the disorder, the more likely that hs-CRP will be higher [16–27]. However, there is substantial variability in the levels of hs-CRP that precludes its clinical use as a diagnostic biomarker, which by the way may be explained by genetic variance in both the CRP and interleukin-6 (IL-6) genes [28]. Nevertheless, because increased hs-CRP may reflect the presence of cognitive deficits, we routinely obtain hs-CRP levels in our clinical practice. As such, if any habitually snoring symptomatic patient has increased hs-CRP (>0.4 mg/dl), we are more likely to recommend treatment even when AHI is not very elevated in the PSG [29]. Similarly, use of hs-CRP before and after treatment may be helpful to guide the clinician as to whether adenotonsillectomy has been successful in normalizing the PSG or whether there is a likely risk for residual OSA to be present [30].

OSA-Associated Inflammatory Biomarkers/ Cardiovascular Biomarkers

As a low degree systemic inflammatory disease, pediatric OSA promotes the activation and circulation of pro-inflammatory cytokines, such as IL-6, interferon (IFN)-γ and tumor necrosis factor alpha (TNF-α). A large number of inflammatory markers have been investigated over the years, but their clinical use remains somewhat uncertain since most of the data relies on single centers, and well-designed multicenter trials are lacking [31–44]. Furthermore, there is also evidence that an important modulator such as vitamin D may be low in certain children with OSA [45].

In addition, altered plasma levels of adropin and B-natriuretic peptide may also provide an indicator of increased endothelial dysfunction, and therefore cardiovascular disease (CVD) risk in children with OSA [37, 46].

OSA-Associated Metabolic Biomarkers/ Metabolic Morbidity Biomarkers

With the global pandemic of obesity in children, OSA plays a significant role in increasing the risk of metabolic syndrome. As a pro-inflammatory and pro-thrombotic state, the major components of metabolic syndrome including insulin resistance, dyslipidemia, hypertension, and hyperglycemia increase the chance of developing cardiovascular disease and type 2 diabetes later in life, and as such detection of such increased risk may allow for earlier and timely intervention [8, 43, 47–52].

Accordingly, in all children undergoing PSG above the age of 4 years, and particularly in those who are overweight or obese (based on BMI z score), a fasting blood draw in the morning after the diagnostic polysomnogram, should be considered. Fasting levels of insulin and glucose, and a complete lipid panel profile including total cholesterol, triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels are not only correlated with the presence of metabolic dysfunction and worthy of attention and intervention (i.e., referral to obesity program, endocrinology, and/or nutritionist) [53–55], but may also be useful as a screening test in children with elevated BMI z scores irrespective of the sleep problem that prompted the referral.

Excessive Daytime Sleepiness in OSA

Evidence suggests that morning plasma TNF-α levels are increased in OSA, primarily due to sleep fragmentation and BMI, and are associated with increased excessive daytime sleepiness. However, there is substantial variability in morning plasma TNF-α levels, which is likely attributable to the presence or absence of the TNF-α-308G gene polymorphism [10, 11, 56–58].

Restless Leg Syndrome (RLS)/Periodic Leg Movement Disorder of Sleep (PLMDS)

Iron-Related Markers

In children with restless leg syndrome and periodic limb movement disorder of sleep, as well as children with restless sleep, serum ferritin levels should be closely monitored, and if so indicated, corrected by supplemental iron treatment. In children with PSG-diagnosed PLMDS and or with clinical diagnosis of RLS, ferritin levels of >50 μg/L, would be a required critical value to improve symptoms [59, 60]. Serum ferritin levels of <45 μg/L had been also linked to abnormal sleep movements, in children with ADHD [61–63], and in autism [64, 65]. More extensive evaluation of iron metabolism may be also indicated and include serum iron, total iron binding capacity, and hepcidin levels [66–69].

Narcolepsy/Idiopathic Hypersomnia/Primary Excessive Sleepiness

Orexin Levels in Cerebrospinal Fluid

Measurement of cerebrospinal (CSF) hypocretin-1/orexin is needed to establish unequivocally the presence of narcolepsy type 1. Hypocretin-1 levels <110 pg/ml have been shown to have very high specificity (~99%) and sensitivity (88–94%) [70–72]. However, other conditions that also may present with REM sleep onset and EDS can exhibit reduced levels of hypocretin-1. Among these, Prader–Willi syndrome has been reported as potentially displaying low levels [73], but exclusion of this genetic condition should be relatively easy unless clinical features are also present.

Some studies have shown the presence of higher CSF histamine (HA) levels together with lower tele-methylhistamine (t-MeHA) levels leading to a significant decrease in the t-MeHA/HA ratios in pediatric patients with narcolepsy type 1 children [74]. Interestingly, some patients with atypical cataplexy may present evolving changes in both CSF hypocretin-1 and HA levels [75]. The value of measuring CSF hypocretin-1 levels in patients without cataplexy is doubtful [76].

Thyroid Panel

In the context of the snoring child, particularly if obesity is concurrently present, one may consider obtaining a thyroid panel to identify whether hypothyroidism may be contributing to sleep-disordered breathing, EDS, or other symptoms [77–79]. However, systematic evaluation of thyroid gland function in pediatric patients with breathing disorders during sleep is not usually recommended or necessary [80–82].

Thyroid evaluation is also usually not recommended in a setting of suspected narcolepsy. However, occasional reports are available of either low levels of thyroid hormone or favorable response and reductions in hypersomnolence in a patient with narcolepsy treated with thyroid hormone supplements [83, 84].

Human Leukocyte Antigen (HLA)-DQB1*06:02

Almost all narcoleptic patients are carriers of this HLA class II allele, while 30–50% of patients with hypersomnia but without cataplexy are carriers and 12–25% of all healthy individuals in carry this allele across different populations [85–90]. Accordingly, the presence of *HLA-DQB1*06:02* in children who also present symptoms of narcolepsy can be a supportive finding in the diagnosis of narcolepsy but is not pathognomonic.

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