Pediatric OSA Syndrome Morbidity Biomarkers

The Hunt Is Finally On!

Leila Kheirandish-Gozal, MD; and David Gozal, MD, FCCP

Since initial reports 40 years ago on pediatric OSA syndrome (OSAS) as a distinct and prevalent clinical entity, substantial advances have occurred in the delineation of diagnostic and treatment approaches. However, despite emerging and compelling evidence that OSAS increases the risk for cognitive, cardiovascular, and metabolic end-organ morbidities, routine assessment of such morbidities is seldom conducted in clinical practice. One of the major reasons for such discrepancies resides in the relatively labor-intensive and onerous steps that would be required to detect the presence of any of such morbidities, further adding to the already elevated cost of diagnosing the disorder. To circumvent these obstacles, the search for biomarker signatures of pediatric OSA and its cognitive and cardiometabolic consequences was launched, and considerable progress has occurred since then. Here, we review the current evidence for the presence of morbidity-related biomarkers among children with OSAS, and explore future opportunities in this promising arena.

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Pediatric OSA syndrome (OSAS) has become a major public health diagnostic entity not only because of its relatively high prevalence,¹ but particularly because of the increased risk for cognitive and behavioral deficits associated with OSAS.²⁻⁴

Furthermore, evidence of cardiovascular involvement manifesting as endothelial dysfunction, systemic and pulmonary hypertension, and alterations in left ventricular geometry and contractility has been reported,⁵⁻⁹ along with heightened risk for metabolic perturbations such as insulin resistance, and dyslipidemias, nocturnal

enuresis, and excessive daytime sleepiness.¹⁰⁻¹⁴ As a result of OSAS, increases in health-care use and costs have been reported,^{15,16} while effective treatment exerts obvious quality-of-life improvements.¹⁷

Current clinical practice heavily and justifiably relies on clinical presentation and physical examination, with overnight polysomnography (PSG) constituting the definitive diagnostic tool.¹⁸ In the usual clinical settings, evaluation for the presence of any of the aforementioned morbidities is seldom if ever performed. Furthermore,

ABBREVIATIONS: CRP = C-reactive protein; CVD = cardiovascular disease; eNOS = endothelial nitric oxide synthase; IL = interleukin; OSAS = obstructive sleep apnea syndrome; MCP-1 = monocyte chemoattractant protein-1; PSG = overnight polysomnography; T&A = adenotonsillectomy

AFFILIATIONS: From the Section of Pediatric Sleep Medicine, Department of Pediatrics, Biological Sciences Division, Pritzker School of Medicine, The University of Chicago, Chicago, IL.

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CORRESPONDENCE TO: Leila Kheirandish-Gozal, MD, Section of Pediatric Sleep Medicine, Department of Pediatrics, Pritzker School of Medicine, Biological Sciences Division, The University of Chicago, 5841 S. Maryland Ave, Office C-113/MC2117, Chicago, IL 60637; e-mail: lgozal@peds.bsd.uchicago.edu

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PSG-derived measurements are only marginally predictive of any of the OSAS-associated morbidities, such that two patients with similar PSG findings may exhibit markedly divergent phenotypes: that is, the presence or absence of end-organ OSAS-related morbidities. The dichotomous clinical morbidity of OSAS, and the extensive clinical burden and cost that would be entailed by systematic exploration of such morbidities, has instigated the search for biomarkers.¹⁹ If accurate and reliable biomarkers of OSAS-related morbidities can be identified and validated, then timely risk stratification and targeted therapeutic interventions can be implemented with a priori optimized outcomes.

Ideal biomarkers for OSAS-associated morbidities should aim to provide information related to prognosis and response to treatment, and should be highly sensitive and specific for OSAS-induced end-organ dysfunction, while also being implicated in an important mechanistic pathway of the disease, so that changes in the biomarker levels during treatment would correspond to parallel changes in end-organ outcome.²⁰ Over the last decade, a constellation of morbidity-related biomarkers has been proposed for pediatric OSAS, and a scoping review was previously published and investigated potential associations and predictive abilities of such published candidate biomarkers in OSAS-induced morbidities in both adults and children.²¹ In this article, we focus on the more promising of such biomarkers, and particularly on those

potentially contributing to detection and monitoring of cardiometabolic morbidity (see [Table 1](#)²²⁻³⁸).

High-Sensitivity C-Reactive Protein and Other Cardiovascular Biomarker Candidates

The concept linking inflammation and pediatric OSAS was initially invoked by Tauman et al³⁹ in 2004. Since then, a large body of evidence has accumulated and confirmed such an association, particularly when concurrent obesity, another chronic low-grade inflammatory disorder, is present.^{32,40-44} Considering the fact that plasma C-reactive protein (CRP) levels appear to be strongly associated with cardiovascular disease (CVD) risk in both adults and children,^{45,46} it was reasonable to postulate that assessment and tracking of CRP levels would provide insights into the clinical course of the disease and response to treatment, as well as enable estimates of CVD risk.⁴⁷ However, although CRP levels manifest dose dependency (ie, CRP levels increase as the severity of OSAS increases, as illustrated by PSG measures), and are responsive to treatment (ie, adenotonsillectomy [T&A]),⁴⁸⁻⁵¹ there was no evidence indicating that they are predictive of measurable CVD risk in children when using other risk assessment measures such as carotid intima-media thickness measurements.^{52,53} Nonetheless, assessments of circulating CRP levels may serve as an indicator of underlying neurocognitive deficits,²² and may also provide an accurate predictor for the presence of

TABLE 1] Summary of Current Biomarker-Based Approaches Aimed at Identifying Increased Risk for Pediatric OSA-Associated End-Organ Morbidities

Candidate Biomarker(s)	Plasma	Urine	Saliva	Reference(s)/Comments
hsCRP	X	...	...	22, 23/predictive of neurocognitive deficits and residual OSA after T&A
Adropin	X	...	...	24, 25/predictive of endothelial dysfunction
MCP-1, MMP-9, PAI-1, and adiponectin	X	...	...	24/use of two or more predicts residual OSA after T&A
TREM-1, pentraxin 3, BNP, MRP 8/14	X	...	...	26-28/associations with endothelial dysfunction ^a
Cortisol and α-amylase	...	...	X	29/a
eNOS SNPs or methylation	X	...	...	30, 31/correlates with endothelial function ^a
LBP, vitamin D, FABP-4, GPR-120	X	...	...	4, 32-37/strong associations with metabolic dysfunction ^a
Epinephrine, norepinephrine, GABA, taurine	...	X	...	38/predictive of cognitive deficits in OSA

BNP = B-type natriuretic peptide; eNOS = endothelial nitric oxide synthase; FABP-4 = fatty acid-binding protein-4; GABA = γ-aminobutyric acid; GPR-120 = G protein-coupled receptor 120; hsCRP = high-sensitivity C-reactive protein; LBP = lipopolysaccharide-binding protein; MCP-1 = monocyte chemoattractant protein-1; MMP-9 = matrix metalloproteinase-9; MRP 8/14 = myeloid-related protein 8/14; PAI-1 = plasminogen activator inhibitor-1; SNPs = single-nucleotide polymorphisms; T&A = adenotonsillectomy; TREM-1 = triggering receptor expressed on myeloid cells-1.
^aPredictive ability remains unexplored.

residual OSAS following T&A.²³ On the basis of the interindividual variability of the responses to T&A we previously found in a large panel of inflammatory markers among a large group of obese children with OSAS,²⁴ it is likely that use of CRP alone, rather than as a component of a multiarray panel, may not provide sufficiently accurate prediction of CVD risk or its resolution with treatment. The issue of multibiomarker-based signatures is discussed further below, but it is critically important to consider such an approach, so as to enable encompassing the interindividual variability in the specific biomarker response to OSAS, which is clearly prescribed, in addition to the disease itself, by both genetic and environmental factors.⁵⁴⁻⁵⁷ In summary, CRP levels emerge as a robust candidate biomarker that definitely merits its inclusion in any future biomarker panel.

Previous work suggested that circulating adropin levels may also provide an indicator of CVD risk in children with OSAS, since children with lower plasma levels appear to be at increased risk for endothelial dysfunction.^{24,25} Indeed, adropin is a 4.9-kDa peptide encoded by the *Enho* (energy homeostasis associated) gene located on chromosome 9; it is important for the maintenance of metabolic and nonmetabolic homeostasis.^{58,59} The gene encoding adropin is involved in the regulation of glucose and fatty acid metabolism, endothelial cell function, and endothelial nitric oxide synthase (eNOS) bioactivity, and as well plays a role in multiple functions in the brain related to physical activity and motor coordination.⁵⁸⁻⁶⁰ Low adropin levels have been reported among patients with diabetes or metabolic syndrome with evidence of cardiovascular impairments.^{61,62} Thus, the biologic plausibility of adropin as a potential biomarker appears to be sufficiently established to warrant future exploration of this candidate biomarker in future multicenter studies.

Considering that nitric oxide-dependent endothelial responses are adversely affected among some but not all children with OSAS,^{5,63-67} and that such physiologic tests likely underlie the early origins of atherosclerosis, improved detection of at-risk children with OSAS seemed justified. Several studies examining other plasma-related candidate markers have been published, including TREM-1 (triggering receptor expressed on myeloid cells-1),²⁶ pentraxin,²⁶ B-natriuretic peptide,²⁷ myeloid-related protein 8/14,²⁸ as well as single-nucleotide polymorphisms in genes such as endothelin and eNOS,³⁰ or epigenetic changes in the promoter

region of eNOS.³¹ Moreover, evidence of disparate responses in endothelial progenitor cell recruitments to the circulation along with similar changes in stromal derived factor-1 plasma concentrations⁶⁸ suggests a complex interplay of coordinated cellular and gene networks contributing to the phenotypic diversity exhibited by children with OSAS. Corroborative evidence of the complexity of such pathways was uncovered through the exploration of plasma extracellular microvesicle microRNAs.^{6,69,70}

As part of our efforts to identify candidate biomarkers for the diagnosis of pediatric OSAS, we explored a prospective cohort of otherwise asymptomatic children, who had received a diagnosis of obesity from their primary care physicians, who underwent extensive clinical evaluation by pediatric sleep physicians along with overnight polysomnography and fasting blood samples at recruitment and 1 year following treatment of either obesity or OSAS if the latter was present (the NANOS study).⁷¹ In this prospective cohort from the community, 75 had received a diagnosis of OSAS (which was defined as an obstructive respiratory disturbance index of 3 events/h total sleep time, based on the Spanish guidelines).⁷² Body mass index, sex, and age were similar in children with OSAS and children without OSAS, and monocyte chemoattractant protein-1 (MCP-1) and plasminogen activator inhibitor-1 levels were significantly higher in all children with OSAS, with interleukin (IL)-6 concentrations being elevated only among the children with moderate to severe OSAS (ie, apnea-hypopnea index > 5/h total sleep time; $P < .01$), while MCP-1 levels were associated with more prolonged nocturnal hypercapnia ($P < .001$).⁷¹ In the follow-up study assessing the impact of therapeutic interventions on these biomarkers, significant declines in MCP-1, plasminogen activator inhibitor-1, matrix metalloproteinase-9, IL-18, and IL-6 occurred along with increases in adropin and osteocrin plasma concentrations.²⁴ When analyzed as a panel, the treatment-responsive biomarkers exhibited excellent sensitivity and moderate specificity to predict the presence of residual OSAS.²⁴ However, the significance of most of these biomarkers relative to cardiovascular outcomes remains uncertain except for the aforementioned changes in adropin plasma concentrations.

Metabolic Morbidity Markers of OSAS

The cumulative evidence strongly supports the presence of metabolic dysfunction, particularly among

obese children with OSAS, manifesting as increased risk for insulin resistance and dyslipidemia.^{11,48,73-78} In this context, increases in low-density lipoprotein and reciprocal decreases in high-density lipoprotein have been inconsistently identified among lean children with OSAS but are more likely to occur in obese children with OSAS.⁷⁹⁻⁸¹ Similarly, evidence of OSAS-associated reductions in systemic insulin sensitivity is now abundantly documented across multiple studies by several groups all over the world. Again, it is worth emphasizing that not all children are affected, and that only a subset of children with OSAS will display such metabolic perturbations. To gain further understanding of potential plasma-based correlates of metabolic dysfunction, we have searched several candidates, including lipopolysaccharide-binding protein,³³ vitamin D,^{32,34} fatty acid-binding protein 4,^{35,36} G protein-coupled receptor 120,³⁷ and circulating T-regulatory lymphocyte populations.⁸² Taken together, it becomes apparent that the magnitude of the systemic inflammatory response is contextually aligned with the risk of cardiometabolic derangements induced by OSAS,⁸³ and that development of prognostic biomarker panels appears justified, provided that such efforts involve large and diverse cohorts.

Cognitive Morbidity Including Excessive Daytime Sleepiness

As mentioned previously, we have found that elevated CRP levels are associated with increased risk for neurocognitive deficits among children with OSAS.²² Such findings were not surprising considering the high degree of concordance between cognitive deficits and endothelial dysfunction.⁸⁴ Preliminary evidence also suggested that the magnitude of the inflammatory response as illustrated by circulating tumor necrosis factor- α may also provide cues as to the presence or absence of excessive daytime sleepiness associated with OSAS.^{13,14,85-87} These early indicators of individual susceptibility are further buttressed by findings showing alterations in the urinary concentrations of a number of neurotransmitters among children with OSAS who were also manifesting evidence of cognitive deficits.³⁸ However, even though the long-term implications of cognitive losses are obviously of great concern, relatively fewer studies have attempted to identify markers of cognitive susceptibility,⁸⁸⁻⁹⁰ most likely because of the labor-intensive nature of psychometric testing and the

relatively large number of children required for such endeavors.^{2,4}

Taken together, it appears that the presence of morbidities that have been thus far associated with pediatric OSAS illustrates the complex interactions between biologic pathways activated by the presence of the disease (eg, inflammation, oxidative stress), environmental factors (eg, diet, physical activity, pollution), and genetic determinants (ie, single-nucleotide polymorphisms in relevant genes involved in the pathophysiology of end-organ dysfunction).⁹¹ On the basis of such a conceptual framework, the vast array of novel technologies that allow for unbiased exploration of an exceedingly large number of prospective biomarkers in relatively small biologic samples should encourage researchers and funding agencies alike to invest in prospective real-life studies aimed at discovering, validating, and implementing biomarkers that reliably detect at-risk pediatric OSAS populations and enable timely and effective interventions.⁹² It is likely that after such proposed multicenter studies that prospectively assess candidate biomarker panels along with polysomnographic characteristics and phenotypic expression of OSA lead to more extensively validated prediction models of end-organ morbidity, the actual implementation in clinical practice should be relatively straightforward and impose only modest incremental costs.

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