COMMENTARY

The Search on an Ideal Disease Marker for Childhood Obstructive Sleep Apnea Syndrome

Commentary on Khalyfa et al. Peripheral blood leukocyte gene expression patterns and metabolic parameters in habitually snoring and non-snoring children with normal polysomnographic findings. SLEEP 2011;34:153-160.

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CHILDHOOD OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS) IS ASSOCIATED WITH SIGNIFICANT NEUROCOGNITIVE AND CARDIOVASCULAR MORBIDITY. Currently, overnight polysomnography is the most commonly available and applied standard test for studying children presented with habitual snoring.[1] Polysomnographic abnormalities include increased apnea hypopnea index (AHI), gaseous exchange abnormalities (intermittent hypoxia, hypercapnia), and sleep disruption (increased arousals). Among these, AHI is the most frequently cited marker for indicating disease severity. Children with AHIs higher than 5 per hour consistently show adverse clinical manifestations in both neurocognitive and cardiovascular axes. Moreover, these manifestations can at least be partially reversed by an effective treatment that reduces AHI to below 1 to 2 per hour. However, the use of AHI is associated with two major limitations. It is still unclear where the clinically valid cutoff for "normal" AHI lies, and whether children with AHI lying between this normal cutoff and 5 per hour should undergo adenotonsillectomy.

Healthy non-snoring children have mean AHIs less than 0.5 per hour of sleep in most studies.[2-4] An AHI of less than 1.5 per hour has often been used as the cutoff of normality (other studies have used AHI cutoffs of 1 or 2 per hour).[1,2,5] The use of AHI of 1.5 per hour as a cutoff has been based largely on statistical normality (in which 1.5 represents the sum of mean and 2 standard deviations in normal children),[2] as well as on anecdotal clinical experience. In this issue of *SLEEP*, Khalyfa and colleagues have provided a long awaited piece of missing scientific evidence in support of the use of an AHI of 1.5 per hour as the cutoff line for normality.[6] Using the RNA microarray technique, the authors found no statistically significant difference in the genome-wide gene expression in peripheral blood leukocyte between normal children and children with primary snoring defined by the presence of snoring and AHI less than 2 per hour.[6] In contrast, the authors found a statistically significant different genome-wide gene expression in peripheral blood leukocyte of children with OSAS, as compared to normal children in a recent study.[7] These results implied that children with primary snoring were essentially normal as measured by the genome-wide pattern of RNA transcription in the peripheral blood leukocytes. The validity of the RNA microarray technique has been shown in various studies.[8,9] The detection of RNA transcription pattern theoretically precedes changes in protein expression, which in-turn should precede other measurable clinical manifestations. Thus, for the first time in childhood OSAS research, there is scientific evidence to support the validity of using AHI of 1.5 or 2 per hour as the cutoff of normality.

The finding of the study[6] also indirectly supports the validity of the earlier finding of the differential gene expression in peripheral blood leukocyte in children with OSAS.[7] These findings represent a significant breakthrough in the search for a potential disease marker for childhood OSAS. Depending on demonstrating acceptable sensitivity and specificity, a unique disease marker may represent a much more simplified and relevant approach in the diagnosis of childhood OSAS in the future.

Childhood OSAS fits into a model of a chronic disease with several important characteristics: 1) variability in disease severity, with potential deterioration during acute upper respiratory infection; 2) individual variation in adverse clinical outcome, which may be related to variable degree of hypoxia and arousals; 3) uncertainty in measurement of disease manifestation due to inherent difference in individual baseline, both in neurocognitive and cardiovascular axes; and 4) potential differences in individual susceptibility.

Currently, there is no simple useful disease marker for childhood OSAS. Ideally, such a marker should be 1) disease specific; 2) present in all patients; 3) reflects the severity of clinical manifestation; 4) reflect the severity of the disease over the cumulative period of the past; 5) show a value with minimum overlap between normal and diseased; 6) display reversibility following proper treatment, regardless of persistence of some degree of end-organ damage; and 7) be detectable before patients develop severe clinical manifestations. By these criteria, most of the currently used clinical and biological parameters, including C-reactive protein, TNF-α, interleukins, insulin, lipid profile, blood pressure, and neurocognitive measures, are all far from being ideal. Further studies along the specific activated pathways evaluated by Khalyfa and colleagues[6] may potentially lead to identification of an easily detectable molecule that can be used as a disease marker for childhood OSAS. This would be particularly useful for clinical management of those children who are currently identified as having "mild OSAS" with AHI lying between 1.5 and 5 per hour. Until then, however, overnight polysomnography

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remains a useful investigation both for clinical use and reference standard in clinical research.

What warrants further validation, is the finding of gene activation in the module involved in adipocyte differentiation/obesity and insulin signaling in children with primary snoring in the study.[6] This finding certainly challenges our current model of understanding of the disease manifestation in childhood OSAS, namely through the mechanisms of intermittent hypoxia and arousals. In this article, the group of children with primary snoring had undisturbed sleep with normal arousal indices and were expected to have very limited frequency of intermittent hypoxia. However, there was already a detectable change in gene set enrichment analysis in genes involved in adipocyte differentiation/obesity and insulin signaling, suggesting that either the threshold for the gene activation was much lower or those changes were operated by yet undiscovered mechanisms.

The RNA microarray technique certainly opens up a new door to research opportunities in childhood OSAS, particularly for enriching understanding of the specific pathways involved in the neurocognitive and cardiovascular morbidity in these children. This represents a promising area for potential discovery of an ideal disease marker for childhood OSAS in the foreseeable future.

DISCLOSURE STATEMENT

Dr. Wong has indicated no financial conflicts of interest.

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