

Editorial

Morbidity of Pediatric Obstructive Sleep Apnea in Children: Myth, Reality, or Hidden Iceberg?



Morbilidad de la apnea obstructiva del sueño en los niños: ¿mito, realidad o iceberg oculto?

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The initial description by Guilleminault et al. of obstructive sleep apnea (OSA) in children included only 8 cases, and all were markedly severe, with enhanced representation of the typical cluster of morbidities related to the disease, and clearly divergent from the current clinical presentation in most pediatric sleep programs.¹ Indeed, even in these early days, the authors already noted “excessive daytime sleepiness, decrease in school performance, abnormal daytime behavior, recent enuresis, morning headache, abnormal weight, and progressive development of hypertension” as phenotypic features of morbidity that should be reversed by treatment of the condition. Four decades later, we find ourselves still casting substantial doubts as to whether a truly causative link exists between the presence of OSA in children and associated morbid features, such as cognitive and behavioral deficits, cardiovascular and metabolic dysfunction, or enuresis.

The major reasons being advanced for this reluctant acceptance of the evidence is predicated on the relatively “disappointing” results of the only randomized controlled trial conducted to date in pediatric OSA, namely the “Child AdenoTonsillectomy Trial (CHAT)”.² This multicenter study enrolled approximately 460 pre-pubertal children and randomly allocated them to early adenotonsillectomy (AT) or watchful waiting (WW), with follow-up assessments at 7 months. The findings showed that although there were significant improvements in the severity of polysomnographic and respiratory alterations, as well as in quality of life and parentally-reported behaviors in the AT group, the main primary outcome, namely neurocognitive function scores did not show significant improvements.² Furthermore, additional post hoc analyses failed to identify any cardiometabolic disturbances responding to AT,³ even if they did indicate that among children with evidence of cognitive alterations, AT was associated with selective improvements in a subset of the neurocognitive battery tests.⁴

How do we reconcile these overall findings with the preponderance of the evidence indicating that sleep-disordered breathing (SDB), even in milder cases such as those corresponding to primary snoring carries an increased risk for aforementioned morbidities?^{5,6} First and foremost, we need to recognize the major limitations of the CHAT trial, and we also need understand the complexities and intricacies of intention to treat analyses in the context of heterogeneity of morbid phenotypes in SDB. In the context of designing the CHAT trial, substantial safety considerations and other factors involved in equipoise of participating investigators led to substantial reductions in the severity of the OSA that would be eligible to participate in the trial. Accordingly, assuming that as the severity of OSA increases, the probability of cognitive deficits will also increase, an assumption that has been corroborated in a large cohort of children,⁷ the proportion of children with such deficits in the CHAT trial would have been smaller than the one regularly encountered in real clinical practice. Secondly, it has become apparent that AT does not necessarily lead to complete resolution of SDB, and that in fact a large proportion of AT-treated children will continue manifesting OSA of varying severity (residual OSA).⁸ Indeed, attempts to delineate predictive biomarkers of residual OSA have been recently proposed.⁹ Accordingly, intention to treat analysis which would include all children in the comparisons between before and after AT would fail to identify significant changes in the cognitive test results, particularly when considering that the efficacy of the procedure is far from perfect. However, we have also learned that there seems to be a much higher proportion of children manifesting behavioral problems in the context of SDB, even when only snoring is detectable in the overnight polysomnographic test.¹⁰ In agreement, significant changes in this particular morbid consequence were detected in CHAT. Based on the anticipated probabilities of any specific morbidity to be present in a given pediatric cohort with SDB, and when accounting for the predicted success rates of AT in normalizing respiratory and sleep measures, intention to treat analyses would only detect significant improvements in cognition following AT if the cohort was a *priori*

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enriched for the primary outcome morbidity being investigated. Alternatively, the cohort size of CHAT would have to be increased several fold to enable detection of significant improvements under such constraints. Another important scenario that has not been considered thus far involves the possibility that assessment techniques used for determination of whether a specific morbidity is indeed present or not may not be sufficiently sensitive to detect the underlying injury in the end-organ. Such serious predicament has recently been evoked in the context of brain imaging studies, whereby evidence for either altered functional brain responses,¹¹ or for actual reduced gray matter in extensive and relevant brain regions,¹² was uncovered in children with OSA and no evidence of cognitive deficits.

What else do we learn from these findings? Since our initial proposal that pediatric OSA comprises at least 2 markedly different phenotypic clusters,¹³ our understanding of this condition has increased, and along with it, the number of such clusters has continued to accrue.¹⁴ Notably, similar trends have emerged in adult patients with OSA. These developments suggest that a multiplicity of modifying factors will operate as determinants of the clinical phenotype, and as a corollary, we need to view pediatric OSA as a finite number of conditions but also by a composite set of scenarios that is accompanied by a myriad of permutations in its clinical presentations and associated morbidities. Considering that in addition to disease severity, both genetic, lifestyle, epigenetic, and environmental elements are operationally involved in the determination of the individual morbid phenotype,^{15,16} there is a pressing need for delineation of a defined panel of clinical and laboratory biomarkers that will enable not only improved accuracy in detection of specific morbidities,^{17–19} but will also allow for better design of clinical trials attempting to definitively seal the current conundrum of whether the relationships between OSA and its putative morbidities are causal or not. Until then, the indications and approaches on whether to treat OSA or wait for its potential spontaneous resolution²⁰ will continue to be reliant on empirical uncertainty. . . Our children clearly and definitely deserve better than that!!

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.arbres.2017.11.013](https://doi.org/10.1016/j.arbres.2017.11.013).

References

- Guilleminault C, Eldridge FL, Simmons FB, Dement WC. Sleep apnea in eight children. *Pediatrics*. 1976;58:23–30.
- Marcus CL, Moore RH, Rosen CL, Giordani B, Garetz SL, Taylor HG, et al. Childhood Adenotonsillectomy Trial (CHAT). A randomized trial of adenotonsillectomy for childhood sleep apnea. *N Engl J Med*. 2013;368:2366–76.
- Quante M, Wang R, Weng J, Rosen CL, Amin R, Garetz SL, et al. Childhood Adenotonsillectomy Trial (CHAT). The effect of adenotonsillectomy for childhood sleep apnea on cardiometabolic measures. *Sleep*. 2015;38:1395–403.
- Taylor HG, Bowen SR, Beebe DW, Hodges E, Amin R, Arens R, et al. Cognitive effects of adenotonsillectomy for obstructive sleep apnea. *Pediatrics*. 2016;138:e20154458.
- O'Brien LM, Mervis CB, Holbrook CR, Bruner JL, Klaus CJ, Rutherford J, et al. Neurobehavioral implications of habitual snoring in children. *Pediatrics*. 2004;114:44–9.
- Li AM, Au CT, Ho C, Fok TF, Wing YK. Blood pressure is elevated in children with primary snoring. *J Pediatr*. 2009;155:362–8, e1.
- Hunter SJ, Gozal D, Smith DL, Philby MF, Kaylegian J, Kheirandish-Gozal L. Effect of sleep-disordered breathing severity on cognitive performance measures in a large community cohort of young school-aged children. *Am J Respir Crit Care Med*. 2016;194:739–47.
- Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, Mitchell RB, Promchiarak J, Simakajornboon N, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. *Am J Respir Crit Care Med*. 2010;182:676–83.
- Bhattacharjee R, Kheirandish-Gozal L, Kaditis AG, Verhulst SL, Gozal D. C-reactive protein as a potential biomarker of residual obstructive sleep apnea following adenotonsillectomy in children. *Sleep*. 2016;39:283–91.
- Smith DL, Gozal D, Hunter SJ, Philby MF, Kaylegian J, Kheirandish-Gozal L. Impact of sleep disordered breathing on behaviour among elementary school-aged children: a cross-sectional analysis of a large community-based sample. *Eur Respir J*. 2016;48:1631–9.
- Kheirandish-Gozal L, Yoder K, Kulkarni R, Gozal D, Decety J. Preliminary functional MRI neural correlates of executive functioning and empathy in children with obstructive sleep apnea. *Sleep*. 2014;37:587–92.
- Philby MF, Macey PM, Ma RA, Kumar R, Gozal D, Kheirandish-Gozal L. Reduced regional grey matter volumes in pediatric obstructive sleep apnea. *Sci Rep*. 2017;17:44566.
- Dayyat E, Kheirandish-Gozal L, Gozal D. Childhood OSA. One or two distinct disease entities? *Clin Sleep Med*. 2007;2:433–44.
- Spruyt K, Verleye G, Gozal D. Unbiased categorical classification of pediatric sleep disordered breathing. *Sleep*. 2010;33:1341–7.
- Kim J, Bhattacharjee R, Khalyfa A, Kheirandish-Gozal L, Capdevila OS, Wang Y, et al. DNA methylation in inflammatory genes among children with obstructive sleep apnea. *Am J Respir Crit Care Med*. 2012;185:330–8.
- Kheirandish-Gozal L, Gozal D. Genotype-phenotype interactions in pediatric obstructive sleep apnea. *Respir Physiol Neurobiol*. 2013;189:338–43.
- Kheirandish-Gozal L, Gozal D. Pediatric OSA. Syndrome morbidity biomarkers. The hunt is finally on! *Chest*. 2017;151:500–6.
- Khalyfa A, Kheirandish-Gozal L, Khalyfa AA, Philby MF, Alonso-Álvarez ML, Mohammadi M, et al. Circulating plasma extracellular microvesicle microRNA cargo and endothelial dysfunction in children with obstructive sleep apnea. *Am J Respir Crit Care Med*. 2016;194:1116–26.
- Khalyfa A, Kheirandish-Gozal L, Gozal D. Circulating exosomes in obstructive sleep apnea as phenotypic biomarkers and mechanistic messengers of end-organ morbidity. *Respir Physiol Neurobiol*. 2017. [http://dx.doi.org/10.1016/j.resp.2017.06.004](https://doi.org/10.1016/j.resp.2017.06.004). pii:S1569-9048(17)30119-2 [Epub ahead of print/Review]. PMID: 28676332.
- Chervin RD, Ellenberg SS, Hou X, Marcus CL, Garetz SL, Katz ES, et al. Childhood adenotonsillectomy trial prognosis for spontaneous resolution of OSA in children. *Chest*. 2015;148:1204–13.