Defining Normal in Pediatric Sleep: Some Thoughts and Things to Think About

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Sleep disorders in general and, more specifically, sleep disordered breathing are highly prevalent conditions in children of all ages. Although the diagnosis of such conditions may seem relatively straightforward in most cases, there are many occurrences whereby symptomatic children undergo diagnostic studies and the results of such tests are interpreted as "normal." We cannot stop but wonder what does "normal" mean in pediatric sleep medicine? The definition of a normal sleep study is not a trivial process, and requires a methodical delineation of representative normative data, clinical and prognostic implications of the demarcation between "normal" and "abnormal," and ultimately demonstration of the effectiveness and reliability of such approaches. Unfortunately, despite major progress in our understanding of many sleep disorders in children, clinically solid and robust normative reference sleep test measures (e.g., polysomnography, polygraphy, actigraphy) are lacking, and more importantly there is no real consensus on any of these important aspects. As such, substantial divergence of opinions among sleep specialists emerge regarding the criteria they use to establish the need or lack thereof of any therapeutic intervention to address the symptoms that prompted the clinical referral to their practices. Such paucity of well-validated data, however, is an opportunity to explore more refined options that ultimately allow for improved personalization and precision in the decision of normal vs. abnormal vs. treatable. For example, incorporation of symptom scores, test results, and critical biomarkers into validated algorithms would yield improved rational for clinical decisions and ultimately better outcomes. There is no doubt that evidence-based approaches to the evaluation of community or clinical referral pediatric populations need to be predicated on scientifically pragmatic and reliable diagnostic approaches that constantly refine the concept of "normal."

The increasing awareness by the medical community and by the public on the importance of sleep along with major advances of sleep medicine over the last several decades, which hopefully have been thoroughly covered in the other chapters of this book, have prompted a high demand for pediatric sleep medicine consultations all around the world. Indeed, the relatively high prevalence of conditions such as obstructive sleep apnea (OSA), periodic leg movement disorder of sleep (PLMDS), or insomnia in the pediatric age range has prompted dynamic and sustained increases in our understanding of their pathophysiology and morbidity. Unfortunately, the herd approach whereby one diagnostic test or one treatment fits all does not work!!!

In the last several years, we have come to realize and so have the parents of our patients that they need a very personalized and precise approach to their sleep problems, and that such precision requires much better definition of what constitutes "normal." For example, emerging data in adults have recently shown that it is not only sleep duration or sleep quality or continuity that determines the presence of end-organ morbidities. In fact, sleep irregularity, that is, how much variability in bedtime and wake-up times is present despite globally the same duration of sleep can lead to markedly divergent risk [1–4]. Irregular sleep schedules have also been associated with higher body mass index, and cardiovascular and metabolic risk in community children [5]. Similarly, when evaluating a large proportion of sleep disorders such as OSA or PLMDS, exclusive reliance on clinical history and physical examination will lead to notorious imprecision in our ability to predict who among symptomatic patients are indeed affected as demonstrated by a sleep study and who are those that notwithstanding the symptoms exhibit a sleep study overnight polysomnogram (PSG) which according to current criteria would be defined as being within normal lim-

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its. In the past, there were those who proposed that every child who is symptomatic, for example, habitually snores during sleep, should be treated without the need for any diagnostic confirmatory test such as a PSG. There are others who have suggested that in the presence of characteristic symptoms and potentially some supportive physical findings, simplified testing procedures could be used such as home-based polygraphy or overnight oximetry [6–23]. We have been among those advocating for such approach, since it has the potential of markedly expanding the availability of testing, and if scalable operations that can become automatic and therefore do not require the onerous and time consuming labor of scoring and interpretation [16, 24–34], then marked reductions in costs can be gained while reserving the pediatric sleep laboratories to those cases in which the diagnosis remains unclear or the clinical presentation is complex and nebulous and therefore more sophisticated diagnostic systems are necessary.

There are those who say that you will know it when you see it to the a priori simple question of whether this child has OSA or PLMDS? Not so fast…! Let's present a scenario where a 4-year-old presents to your sleep clinic referred by their primary care physician because parents have complained that the otherwise healthy child except for seasonal allergic rhinitis, snores almost every night, has frequent scary nightmares, and is often grumpy in the morning. We could adopt a frequently applied answer to the question: how do you know that this symptomatic child before you in clinic does not need any treatment because his PSG is normal? Indeed, if the apnea-hypopnea index (AHI) of this child is less than one per hour total sleep time (TST), we will tell the parents that the PSG is normal, and this is the end of the visit. However, the child came to be evaluated because of significant symptoms, and the fact that the sleep study is normal does not necessarily indicate that this child is healthy and does not suffer from a sleep disorder.

What cutoff values of AHI, oxyhemoglobin desaturation index (ODI) 3%, periodic leg movement index (PLMI), etc., should we then adopt as demarcating normal from pathological? Should we use statistical classifiers? In such instance, should we adopt 2, 3, 5 standard deviations beyond the mean of the sleep measure as obtained from a representative cohort of healthy community children spanning over the whole pediatric age range to determine that that measure is pathological and requires treatment? How would such set of rules affect the decision algorithm and how many symptomatic children would be excluded from the "abnormal" ergo has "disease" category? These are difficult issues because there is very little correlation between the phenotypic expression and severity of the sleep disorder (i.e., the reported or measurable severity of symptoms, signs, and disease-associated morbidities) and the actual polysomnographic measures by which we currently define that the test is "abnormal."

For example, let's take excessive daytime sleepiness (EDS) in children with habitual snoring who underwent PSG evaluation. It is clear that a proportion of children with OSA manifest loosely defined EDS and that as the severity of OSA increases (as defined by ether increasing AHI, increasing severity of hypoxemia, or enhanced sleep fragmentation), the probability of exhibiting EDS is also increased [35–39]. However, symptoms and physical findings do not assist with the decision of whether OSA is present or not [40]. Furthermore, if you ask the parents of snoring children, the prevalence of EDS using a sleepiness questionnaire such as the modified Epworth score is relatively low ranging between 8 and 15% [41–54], even though when EDS is present, it is more likely that OSA is also present, that is, EDS adds specificity at the expense of sensitivity [55, 56]. Moreover, if EDS is evaluated more objectively using the Multiple Sleep Latency Test (MSLT), then only a small proportion of children will exhibit mean sleep latencies <10 min and such proportion is augmented as the severity of sleep-disordered breathing is increased [35], or more particularly when children are obese [57]. In light of the marked variability in the expression of EDS among snoring children or even among those fulfilling criteria for moderate to severe OSA, and the fact that EDS as defined by MSLT results could be definitely present even in children with snoring but otherwise statistically normal PSGs, we attempted to identify other PSG-derived measures that may predict increased sleep propensity in habitually snoring children. One of such efforts involved looking at respiratory-related arousals relative to spontaneous arousals, and indeed, evidence of dynamic regulation of arousals emerged whereby spontaneous arousals were likely to progressively decline when increased frequency of respiratory arousals took place up to a certain limit at which time it would seem that the compensatory capacity to accommodate sleep fragmentation induced by sleep-disordered breathing was exceeded and therefore it would be reasonable to assume that sleepiness would be more likely to emerge [58]. Interestingly, the cut-off AHI at which this phenomenon of "compensatory decompensation" seemed to become manifest was between five and seven events per hour TST, and this figure will recur in our subsequent discussion below. The corollary to this observation was that there should be some biological measures that could more objectively serve as accurate reporters of EDS, and circulating levels of tumor necrosis factor α (TNF) were proposed with variable success, likely related to genotypic variance [59–63]. Therefore, we will be confronted with a clear conundrum: Assuming proper sleep hygiene and sleep duration by these two families, a snoring child with a AHI <1/hour TST and significant sleepiness (falling asleep at school and at home) and a snoring child with a AHI >5 hour TST without any evidence of EDS. All of us would treat the latter but would feel very

ambivalent about treating the former. It is through examples like this that we come to the realization that: (i) the large variability of the phenotypic expression of a sleep disorder in children; (ii) the relatively limited value of current PSG-derived measures to guide treatment decision or to predict morbidity.

The problems raised by the inaccuracy of PSG-derived measures and cut-offs to demarcate disease (i.e., morbidity) are not only limited to EDS, but also affect many other putative consequences of sleep disorders. Indeed, even though we reported that there was a positive and significant association between the probability of cognitive deficits and the standard PSG measures (AHI, nadir SpO_2, respiratory arousal index) [64], the frequency of weekly snoring (nights per week) emerged as a stronger predictor of a composite cognitive measure than the AHI [65]. Of note, the AHI cut-off at which the probability of cognitive deficits increases is also situated around five to seven per hour TST, and that the negative findings related to the absence of significant improvements in cognitive function in the only randomized trial to date, the children adenotonsillectomy trial (CHAT) study can be simply explained by the absence of sufficient power to identify such improvements when the majority of the children who participated in the trial had a priori and unsurprisingly normal cognitive function [66]. Indeed, such cognitive batteries are designed to detect and diagnose children with substantial losses (i.e., developmental delay) and with standard deviations that are 10–15% of the whole scoring range it is not surprising that small improvements may not be detectable. We will also remark that cognitive assessments are not a routine part of any of the clinical evaluations we perform in the Pediatric Sleep Clinic, and that the only information we gather is how the patient is overall doing academically if they are of school age.

To search for solutions, let us therefore enumerate the list of issues and problems that the field of pediatric sleep medicine will have to resolve in the upcoming years:

- How do we define a "normal' PSG? [67–74]
- Does PSG contain embedded prognostic and morbidity-related information (biomarkers) that can be extracted using artificial intelligence and deep learning approaches? [75–78]
- Identifying simplified and optimized diagnostic approaches that are scalable and reliable [24–32, 79, 80].
- Delineating additional clinical features that enable patient diagnostic and therapeutic decisions [81, 82].
- Identifying potential biomarkers that promote a better understanding of the phenotype and the response to therapy [83–89].
- How do we enable precision medicine in pediatric sleep medicine? [90]

As mentioned in the introductory lines, the field of pediatric sleep has achieved remarkable growth and expansion in both scientific content and clinical know how. However, the empirical trajectory that has brought us this far is proving insufficient as far as addressing important discrepancies between the findings in our very expensive diagnostic workhorse (i.e., PSG) and clinical decision making. As we continue evaluating children with sleep-related issues in our clinics, we need to be reminded of the list of issues that remain unresolved and keep a healthy and skeptic approach when confronted with discrepancies between the symptoms and the findings of the diagnostic tests we have used. In the words of the famous and erudite physician Maimonides (AD 1137–1204):

The more accomplished one is in that science, the more precise his investigations are, the more doubts and difficult questions arise in him. He will go into additional investigations and will hesitate in some of his answers [91].

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