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Genotype–phenotype interactions in pediatric obstructive sleep apnea☆

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ABSTRACT

Pediatric sleep disordered breathing (PSDB) is not only a very frequent condition affecting 2–4% of all children, but is also associated with an increased risk for a variety of manifestations underlying end-organ injury and dysfunction that impose both immediate and potentially long-term morbidities and corresponding inherent elevations in healthcare costs. One of the major problems with the creation of valid algorithms aiming to stratify diagnostic and treatment prioritization lies in our current inability to predict and identify those children who are most at-risk for PSDB-induced adverse consequences. Thus, improved our understanding of the mechanisms governing phenotype variance in PSDB is essential. Here, we examine some of the potential underpinnings of phenotypic variability in PSDB, and further propose a conceptual framework aimed at facilitating the process of advancing knowledge in this frequent disorder.

1. Pediatric sleep disordered breathing (PSDB)

Obstructive sleep apnea syndrome (OSA) is a common condition in children affecting up to 2–4% of all children with a peak incidence between 1 and 8 years of age (Kaditis, 2012).

Increased upper airway resistance or periodic obstructions of the upper airway during sleep lead to increased intrathoracic inspiratory pressures, intermittent oxyhemoglobin desaturations that are usually accompanied by $PaCO_2$ elevations, and promote the disruption of sleep integrity as manifested by EEG arousals, ultimately enhancing the risk for excessive daytime sleepiness, as well as multiple other associated morbidities (see below) (Gozal, 2000; Gozal et al., 2010; Gozal and Kheirandish-Gozal, 2009).

2. Pathophysiological mechanisms in PSDB

It is now clear that no single causative factor can be ascribed as solely responsible for the occurrence of OSA. However, the interplay between 4 major factors may in fact account for the vast majority, if not for the totality of the cases in otherwise healthy children. More specifically, interactions between craniofacial and anatomical factors, lymphoid tissue growth patterns, upper airway inflammation, and neuromuscular reflexes appear to underlie the emergence of OSA. Taken together, these elements lead to a pharyngeal airway of reduced dimensions that also exhibits an increased collapsibility, particularly during sleep. Indeed, awake children with OSA demonstrate the ability to compensate against the collapsible forces, primarily through recruitment of upper airway dilator muscles that maintain airway patency, and upper airway constrictors that enable increased upper airway rigidity (Arens and Marcus, 2004). Upon sleep onset, these compensatory mechanisms are dampened, and the underlying upper airway collapsibility becomes manifest, leading to CO_2 retention (resistive loading and obstructive alveolar hypoventilation), lowered PaO_2, and increasing respiratory effort, all of which are resolved upon the occurrence of cortical or sub-cortical arousals, the latter promoting sleep fragmentation and non-restorative sleep. Cephalometric surveys of children with OSA have overall suggested the presence of selected alterations in the dimensions and vectors of several craniofacial skeletal structures (Kawashima et al., 2002; Marino et al., 2009). For example, children with OSA are more likely to display mandibular retrognathia, smaller maxillary dimensions, greater posterior facial height, reduced maxillary protrusion and growth, and shorter and flattened dental arches (Shintani et al., 1996). Kawashima et al. (2002) evaluated the dentofacial morphology and the pharyngeal airway space in preschool children with OSA, and found that children with OSA had mandibular retrognathia and narrower pharyngeal airway space, while Marino et al. (2009) evaluated the craniofacial cephalometric features of preschool children with OSA using measurements derived from lateral cephalometry, and identified skeletal Class II patterns with retrognathic mandible

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and increased skeletal divergency among children with OSA. In contrast, Arens et al. (2001) were unable to replicate these findings, whereby the mandibular width, length, and volume were not different from in children with OSA when compared to control subjects. In a subsequent study that employed 3-dimensional reconstruction techniques, no significant differences in mandibular size and shape were identified among 24 children with OSA and 24 matched controls (Schiffman et al., 2004). Thus, substantial variance appears to exist as far as the presence of altered maxillo-mandibular measures along with the growth patterns of other craniofacial structures, and less than optimal understanding is currently present as to who these elements interplay to contribute to upper airway growth and function.

Adenotonsillar hypertrophy has been considered as the most important driver of risk for the occurrence of PSDB. However, the mechanistic pathways underlying normal and abnormal follicular lymphoid tissue proliferation and hyperplasia remain hitherto unknown. Furthermore, our understandings of the inflammatory processes within the upper airway that contribute to OSA occurrence or result from the presence of PSDB are still extremely poorly understood. In recent years, it has become apparent that an array of environmental or tissue-derived stimuli may lead to accelerated proliferation of lymphadenoid tissues within the upper airway, and that such processes trigger an inflammatory response, the latter being most likely implicated in the pathophysiology of PSDB. Accordingly, alterations in local (i.e., upper airway) and systemic inflammatory markers have been consistently reported in children with OSA (Li et al., 2007; Gozal et al., 2008; Goldbart et al., 2006; Kaditis et al., 2009; Shen et al., 2011), thereby suggesting that inflammation is an important precipitating risk factor for OSA. For example, increased expression of cysteinyl leukotrienes and changes in glucocorticoid receptor expression and activity have been reported by several investigators in the adenoids and tonsils of children with OSA, and putatively assigned a mechanistic role in the induction of hyperplasia and hypertrophy of these upper airway tissues (Goldbart et al., 2004; Kaditis et al., 2008; Goldbart et al., 2005; Tsaoussoglou et al., 2012).

In addition, initial epidemiologic evidence implicates respiratory viruses and airway irritants, e.g., exposure to cigarette smoke, to increased propensity for development of adenotonsillar hypertrophy (Goldbart et al., 2007; Snow et al., 2009; Castaneda et al., 2012). Furthermore, the co-existence of inflammatory processes in the context of airway disorders such as rhinosinusitis, allergic rhinitis, or asthma is not only higher in PSDB as compared to the prevalence in the general population, but appears to affect the severity of PSDB as well, thereby, suggesting possible interactions between inflammatory mediators released in the airway by these conditions and promotion of proliferation of lymphatic tissues (Ersu et al., 2004; Kheirandish-Gozal et al., 2011; Malakasioti et al., 2011; Ross et al., 2012). Further confirming the above mentioned assumptions, we have previously shown that T cell lymphocytes are in a highly proliferative state in the tonsils of children with OSA, and display increased production of pro-inflammatory cytokines, such as IL-1α, TNF-α, and IL-6 (Kim et al., 2009). Taken together, it is very plausible that an array of environmental factors, such as viruses or air pollution, may alter the typical milieu of the upper airway, and lead to local inflammatory responses that then result in mucosal swelling, lymphadenoid tissue proliferation, and culminate in upper airway obstructive events during sleep. Application of unbiased bioinformatic approaches of the transcriptome to decipher potential pathways associated with adenotonsillar proliferation in PSDB revealed that processes underlying inflammatory signaling, immune regulation, and immune tissue growth and remodeling are distinctly dysregulated in upper airway lymphoid tissues of children with OSA (Khalyfa et al., 2010a,b).

In addition to the robust evidence implicating anatomic abnormalities and inflammatory processes in pediatric OSA, alterations in neuromuscular reflexes may also contribute and promote the increased airway collapsibility that characterizes PSDB. As a corollary to such assumption, we should point out that children with markedly enlarged tonsils and adenoids may present a completely normal polysomnographic pattern, while the reverse, i.e., relatively small tonsils and adenoids may be accompanied by markedly severe OSA. Furthermore, most children with OSA do not snore during wakefulness, and surgical extirpation of adenotonsillar tissues is not always accompanied by complete resolution of OSA (Bhattacharjee et al., 2010). Taken together, alterations in neuromuscular reflexes may underlie an important component of the risk for OSA, and indeed pediatric patients with OSA universally show altered active and passive properties of the upper airway during sleep (Marcus et al., 2004; Gozal and Burnside, 2004). More recently, studies employing computational fluid dynamic techniques interfaced with upper airway imaging suggest that higher airflow resistance is consistently present in the upper airway of children with OSA (Xu et al., 2006; Mihaescu et al., 2008).

In summary, the integrated interactive presence of varying degrees of nasal flow resistance, craniofacial characteristics, altered tissue size or mechanical properties, and neuromuscular deficits are critical components of the equation that will resolve the level of OSA risk for any given child. A missing ingredient to this equation is the degree of genetic contribution to the risk, and this area has only recently begun to be explored, particularly after family-based studies revealed the clustering of OSA (Redline et al., 1992).

3. Morbid consequences of OSA

It should not be surprising to anyone that the major impetus driving the investigation of any given condition is the fact that such condition promotes the occurrence of adverse complications. In the last 3 decades, an ever growing number of studies have revealed significant associations between PSDB and multiple end-organ morbidities, primarily affecting CNS, cardiovascular, and metabolic systems (Gozal and Kheirandish-Gozal, 2012). A cardinal observation pertaining to any of these associations is the irrefutable fact that at any given level of PSDB severity, there is a fraction that manifests no evidence of morbidity. Conversely even in the presence of extremely mild PSDB, there is a subset of children that exhibits prominent morbidity. One putative explanation for the presence of such phenotypic variance may reside in the underlying presence of genetic variance, i.e., the presence of single nucleotide polymorphisms in specific genes that may account for the differential end-organ susceptibility in PSDB (Fig. 1).

4. Genetic determinants of morbidity in PSDB

It is rather unfortunate that the field of genetic exploration of PSDB is really in its infancy. Indeed, only a limited number of reports on the associations between specific gene polymorphisms and PSDB-associated morbidity is currently available, but such preliminary findings further buttress the validity and the need for large population-based genome-wide association studies (GWAS) in this area.

4.1. Apolipoprotein E

Apolipoprotein E (ApoE) is a lipoprotein synthetized in the liver and brain that regulates components of cellular cholesterol deposition and transport. Apolipoprotein E (ApoE) exists as 3 alleles: ε2 (E2), ε3 (E3), and ε4 (E4), with the latter displaying reduced biological activity. Consequently, excess of ApoE4 allele frequency