Correspondence

INOSA Guidelines in the era of precision medicine

Sir,

Sharma and his co-authors are to be congratulated for their excellent and comprehensive suggested first edition of the INdian initiative on Obstructive Sleep Apnoea (INOSA) guidelines published in 2014. Since the guidelines are described as “evidence-based”, without denigrating the quality of their work, the purpose of the present letter is to add a few remarks on two issues briefly touched in these guidelines, which should further enhance justifications of such evidence-based guidelines. These remarks may also be of value to make the guidelines potentially “individualized”, since there is a global shift of paradigms of detection, management and treatment of medical problems of significant public health burden through initiatives such as “precision medicine”.

Since the basic premise of precision medicine is to take into account individual variability in developing strategies of prevention as well as treatment of diseases, the role of genetic predisposition is to be emphasized as a risk factor of obstructive sleep apnoea (OSA) as well as its associated syndromes (OSAS), mentioned in Table II of the guidelines paper. Our own data as well as reviews and notes published on this subject suggest that candidate gene regions that are shown to be associated with OSA and/or OSAS are not of mere statistical significance detected through epidemiological case-control studies; they have their functional relevance as well. For example, associations of OSA/OSAS with polymorphisms at the peroxisome proliferator-activated receptor-γ (PPARG), and glucagon receptor genes directly explain the co-morbid relationship of OSA/OSAS with centralized obesity, since polymorphisms at these two gene regions are also associated with central adiposity. Likewise, the Leptin (LEP) gene is a critical regulator of adipose tissue mass of body weight, and it operates by inhibiting food intake and stimulating energy expenditure (both of which are involved in mechanistic pathogenesis of obesity). Consequently, the association of LEP polymorphism with OSA/OSAS is likely to be more than of only statistical significance. The association of APOE polymorphisms with OSA/OSAS could be through the functional involvement of APOE in neurological degeneration and dyslipidaemia. For such reasons, these genes were listed as candidate genes for OSA/OSAS. In terms of management and treatment of OSA and its associated co-morbid conditions, identification of such genetic risk factors has at least three important implications. First, such candidate gene discoveries can help in defining phenotypes that may serve as intermediate phenotypes of OSA, which may be used as indicators of more readily treatable precursors or consequences of OSA/OSAS. In this context, it is worthwhile to note that several of the morbid conditions (listed in Table III of the guidelines paper) as well as the ones we detected, may be precursor intermediate phenotypes of OSA rather than being consequences of OSA. Irrespective of this, genes underlying such phenotypes would also be the foci of familial hereditary risk factors of OSA/OSAS. This would also help in more precise (and perhaps individualized) diagnosis of OSA, since the algorithm for diagnosis (depicted in Figure 2 of the guidelines paper) can be revised by incorporating such intermediate phenotypes. Second, genes underlying correlated phenotypes also serve as therapeutic targets for management and treatment for majority of such phenotypes. In the area of cancer treatment, with the use of The Cancer Genome Atlas (TCGA) data, such efforts have been proven to be useful in identifying tissue- or mutation-
specific functions of proteins that may be targeted for inhibiting development and progression of otherwise aggressive cancers\(^8\). Third, the precise sites of gene associations would allow clinical investigations with respect to ‘individual-specific’ modalities of treatment for OSA/OSAS. For example, individual genotypes at the single nucleotide polymorphism (SNP) sites rs15780, rs405509, rs769455 and rs7412 of the \textit{APOE} gene, that are associated with OSA\(^3\) can be tested to examine if the suggested measures for treating OSA (see Box 5 of the guidelines paper\(^1\)) work equally well for individuals who are genetically predisposed as compared to others. Similar genotype-specific efficacy studies of different types of positive airway pressure (PAP) can also be performed to examine which type of PAP-therapy works better in individuals who are genetically predisposed for OSA-risk.

The second issue that may be further discussed relates to surgical treatment of OSA. We conducted a retrospective analysis of pre- and post-operative (for weight-loss) polysomnographic data from adolescents with severe obesity\(^9\). We observed a marked improvement in sleep efficiency and sleep fragmentation with surgical weight loss, which is consistent with the suggestions made in section 5 of the guidelines paper\(^1\). However, it may be emphasized that there is now emerging evidence that surgical weight loss results in improvement in quality of life\(^6\), through resolution of obesity-associated psychosocial, metabolic, and cardiovascular morbidity. Consequently, it may be suggested that correction of sleep fragmentation could be an important but as yet underappreciated factor influencing changes in other major comorbidities of obesity, including OSA/OSAS.

In summation, Sharma \textit{et al}\(^5\) provided a basis of INOSA guidelines that may be further substantiated to attempt diagnosis, management and treatment of OSA and its associated medical adversities, in which evidence-based individualized characteristics of patients may be incorporated for reducing the public health burden of this sleep disorder.

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\textbf{References}