The potential impact of family history of loud Snoring and risk of Obstructive sleep apnea in overweight subjects.

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ABSTRACT

Context: Central obesity, increased neck circumference are strong established risk factors of OSA. Familial aggregation is less explored potential risk factors. **Aims:** To compare sleep, metabolic parameters and risk of OSA in subjects with and without history of loud snoring in first degree blood relatives. **Settings and Design:** Cross-sectional tertiary hospital-based study **Methods and Material:** Overweight subjects (body mass index >25 kg/m2 aged 18-65 yrs were selected using systematic random sampling from attendants of patients attending Pulmonary Medicine OPD .On the basis of inclusion and exclusion criteria,380 subjects were enrolled, inquired about "Loud Snoring" in their first degree blood relatives and full night study, fasting serum lipid profile, plasma glucose level estimation was carried out after taking informed/written consent. **Statistical analysis used:** Statistical analysis was performed using SPSS 20. Student t test was applied for comparing mean values of various variables between two groups. Fisher test was applied for estimation of odd ratio (OR). **Results:** Neck circumference (p value .01), AHI value (p value .01) and fasting plasma glucose levels (p value .04) were found significantly higher in subjects with positive history of loud snoring in any first degree blood relative . Increased but insignificant risk (P value 0.15) of OSA (defined as AHI<5); OR 1.7 (range .8-3.6 with 95% CI) was observed in these subjects when compared on the basis of presence or absence of history of loud snoring in any first degree blood relative . **Conclusion:** This study gives us a new direction for determining potential role of family history in near relatives in progression and occurrence of OSA in an individual.

Key words: Familial aggregation, Obstructive Sleep Apnea , Obesity, snoring.

INTRODUCTION

Recurrent collapse of the upper airway occurs in Obstructive Sleep Apnea (OSA) leading to snoring, repeated episodes of sleep disturbances, hypoxemia, hypercapnoea, variations in intra-thoracic pressure and increased sympathetic activity.[1]

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According to the epidemiological, community based studies from various parts of India, prevalence of OSA Syndromes (OSAS) is found to be somewhere around 2.4% - 4.9% in men and 1% - 2 % and in women[2-6] comparable to the prevalence of OSAS worldwide.[7,8]

The demographic characteristics that predispose to development of OSAS include age, male gender, pregnancy and post-menopausal state. Strong established risk factors of OSA occurrence include obesity, central body fat distribution, increased neck circumference and several craniofacial region and upper airway anatomical abnormalities.

Other potential risk factors include genetic predisposition, familial aggregation, tobacco smoking, alcohol addiction, nasal congestion during night, endocrine abnormalities (hypothyroidism, acromegaly), polycystic ovarian syndrome, Down's syndrome and few drugs (benzodiazepines, muscle relaxants, testosterone therapy). [9, 10]

Familial aggregation and genetic factors are thought to play a role in the development of OSA. The genetic factors influence the anatomical factors (craniofacial structure, upper airway soft tissues, body fat distribution).[11] As obesity is closely associated with OSA, these genetic factors influencing obesity have also been thought to influence the familial clustering of OSA.[12] to best of our knowledge, familial gathering of OSA and its effect on predisposing factors and associated conditions like obesity, central obesity, neck circumference, hypertension, plasma blood sugar level, serum total cholesterol, HDL and triglyceride have not been properly studied. One large (n = 3470) questionnaire based study[13] was done in Pakistan in which Family history of snoring was observed one of significant risk factors (OR 2.9, 2.5-3.5) for OSA symptoms along with age, body mass index, collar size, nasal blockage. OSA is common in patients with craniofacial disorders; however, even in individuals without a specific disorder, alterations in craniofacial structure confer risk for OSA. This is particularly significant in patients of Asian descent .[14]

This study was done to find out risk of occurrence of OSA and comparison between obesity, sleep and metabolic parameters in overweight subjects with and without history of loud snoring in first degree blood relatives.

SUBJECTS AND METHODS

We conducted a cross sectional tertiary hospital-based study in Lucknow, India, from April 2011 to June 2014 after approval from Institutional Ethical Committee (IEC). Five hundred and nine Overweight Subjects (body mass index >25 kg/m^2) males and females aged 18-65 yrs participated .Patients were selected using systematic random sampling from attendants of patients attending Pulmonary Medicine OPD every Saturday(five per week). The purpose of study was explained to all the subjects and three hundred and eighty subjects (300 males and 80 females) agreed to participate (participation rate 72.2%); all these subjects were enrolled after taking informed/written consent. Subjects with history of Liver disease, Chronic Obstructive Pulmonary Disease (COPD), uncontrolled Asthma, Cancer, End Stage Renal Disease, heart failure and any other endocrine disorder (except type 2 diabetes mellitus) like Cushing syndrome and thyroid abnormalities were excluded from the study.

HISTORY OF LOUD SNORING

Subjects were inquired specifically as a previous study[15] about presence of "Loud snoring" (i.e. "Tez Kharrate" in Hindi language translation) in their first degree blood relatives.

EXCESSIVE DAY TIME SLEEPINESS

Epworth Sleepiness Scale [16](ESS) was used for subjective measurement of sleep tendency during daytime. In this tool, subjects rate the probability of dozing off in eight different situations that are met in day-to-day life on a scale of 0-3. Thus, the sum of the score can vary from 0 to 24.

POLYSOMNOGRAPHY

All subjects underwent full night polysomnography sleep study (S-7000, Cogent technologies, EMBLA System Inc). The parameters studied were Electroencephalograms (EEG), (C3-A2, C4-A1, O2- A1, O3-A2), ECG and O_2 Saturation measurement by finger Pulse oximeter. Apnea Hypopnea Index (AHI) was calculated with the help of Somnologica Studio software. The apnea episodes were defined as complete cessation of airflow for ≥10 seconds. A hypopnea is defined by the presence of a clear decrease in the amplitude of airflow (quantitative or semi-quantitative) of >30% from baseline during sleep or aclear amplitude reduction of a valid measure of breathing during sleep that does not reach the above criterion, but is associated with either an oxygen desaturation of>3% or an arousal and the event lasts 10 seconds or more.[17]AHI was determined by the frequency of these events per hour during sleep time based on the results of the overnight polysomnography. Recorded Polysomnographic data was cross checked manually for scoring of sleep stages, apneas and Hypopnea events regarding each subject.

BIOCHEMICAL ANALYSIS

Fasting venous blood samples (3 ml) were taken in plain (2 ml) and in fluoride vial (1 ml) just after and within 30 minutes of completion of the overnight polysomnography study. Serum lipid profile (Total Cholesterol, Triglyceride and HDL-C) and Fasting Plasma glucose estimation was done by enzymatic method (Merck) using Microlab Semi-autoanalyzer (Merck, Germany). LDL and VLDL calculated by Friedweld formula.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 20(SPSS Inc, USA). After assessing for approximate normal distribution, all continuous variables were summarized as mean±SD and categorical variables were expressed as n (%). Student t test was applied for comparing mean values of various variables between two groups. Fisher test was applied for estimation of odd ratio (OR).

RESULTS

Gender distribution and Mean values for anthropometric parameters BMI, Neck circumference, Waist Circumferences, HC ,WHR, Sleep Structure parameters N1, N2 ,N3, Rapid eye movement (REM) sleep, Total Sleep Time (TST), Sleep Sleep Efficiency, sleep onset time and Sleepiness and polysomnographic findings have been described in Table 1,2,3 and 4 respectively.

Occurrence of Family history of loud snoring in First degree blood relative was significantly higher (P value 0.02) in males with Odd ratio of 2.1 (range 1-4.4 with 95% CI) in studied population (Table 5,6). Increased but insignificant risk (P value 0.15) of occurrence of OSA (defined as AHI<5) with Odd ratio of 1.7 (range .8-3.6 with 95% CI) was

Table 1: Gender distribution of the subjects

Gender	Subjects (n)(%)	BMI (Mean ± SD) (Range)
Male	300(78.9)	31 ± 4 (25-44)
Female	80(21.1)	33.8 ± 5.2(25-50)
Total	380(100)	31.6 ± 4.5 (25-50)

Table 2: Anthropometric values (mean ± SD) of the subjects

Anthropometric Parameters	Subjects (n=380)	Minimum	Maximum
BMI (kg/m²)	31.6 ± 4.5	25	50
Neck circumference (inches)	16 ± 1.5	12.1	20
Waist Circumferences (centimetres)	109.9 ± 109.9	84	145
HC(centimetres)	104 ± 8.6	86	143
WHR (ratio)	1.05 ± 0.06	.82	1.25

Table 3: Sleep Structure parameters (mean ± SD) of the subjects

Sleep Structure Parameters	Subjects
N1(%Total Sleep Time)	19.8 ± 15.4
N2(%Total Sleep Time)	34.5 ± 21.9
N3 (%Total Sleep Time)	26.8 ± 25.5
REM (% of Total Sleep Time)	18.7 ± 17.7
Total Sleep Time (minutes)	410.8 ± 115.7
Sleep Onset (In minutes)	27.3 ± 25.5
Sleep Efficiency (%)	82.2 ± 14

Table 4: Sleepiness and polysomnographic parameters (mean ± SD) of the subjects

Sleep variables	Subjects (n=372)
Epworth Sleepiness Score (ESS)	11.7 ± 5.4
Apnea Hypopnoea Index(AHI; per hour)	37.6 ± 30.8
Obstructive eventsl (per hour)	26.4 ± 27.6
Hypopnea events (per hour)	8.3 ± 9.5
Desaturation Fall<5% (in minutes)	36.7 ± 29.4
Mean Pulse[bpm]	75.8 ± 16.7
Min Pulse[bpm]	56.1 ± 11.4
Max Pulse[bpm]	106.5 ± 25
Average Oxygen Saturation (%)	92.2 ± 5.2
Lowest Oxygen Saturation (%)	76 ± 12.5
Average Desaturation (%)	7.8 ± 3.7
Sp O2 <90%	22.1 ± 29.7
Oxygen Desaturation events (OD; per hr)	36.3 ± 29.6

Table 5: Family history of loud snoring in First degree blood relative

Family history	Gender		Total
	Male	Female	
Positive	172	31	203
Negative	128	49	177
Total	300	80	380

Table 6:Risk of occurrence of Loud Snoring

Odds Ratio for Family snoring category (Yes / No)	Value	95% Confidence Interval		P value
	2.1	Lower	Upper	
		1	4.4	0.02

Table 7: Family history of loud snoring in first degree blood relative

Family history	Case AHI level >5	Control AHI level <5	Total
Positive	132	40	172
Negative	170	30	200
Total	**302**	**70**	**372**

Table 8:Risk Estimate for OSA against Snoring in first degree blood relative

Odds Ratio for Family Snoring Category (Yes / No)	Value	95% Confidence Interval		P value
		Lower	Upper	0.15
	1.7	0.8	3.6	

Table 9: Comparison of various variables in subjects with and without Family history of snoring

Variables	Family snoring Category	Mean±SD	Significance. (2-tailed)
AGE	Yes	47.8 ± 9.5	.22
	No	49.5 ± 9.7	
BMI	Yes	31.8 ± 4.8	.40
	No	31.3 ± 4.1	
NC	Yes	16.3 ± 1.5	.01
	No	15.7 ± 1.4	
WC	Yes	111.2 ± 11.8	.07
	No	108.2 ± 11.8	
HC	Yes	105 ± 9	.08
	No	102 ± 8	
WHR	Yes	1.05 ± .06	.43
	No	1.05 ± .07	
Systolic Blood Pressure	Yes	136.4 ± 15.2	.93
	No	136.6 ± 15.8	
Diastolic Blood Pressure	Yes	87.9 ± 8.6	.97
	No	87.9 ± 9.8	
AHI	Yes	42.5 ± 32	.01
	No	30.9 ± 28	
HDL	Yes	42.4 ± 7.9	.35
	No	43.7 ± 10.6	
LDL	Yes	119.8 ± 47	.30
	No	112.5 ± 45.7	
VLDL	Yes	32.4±13.7	.98
	No	32.4±16.7	
TG	Yes	162.6±68.6	.98
	No	162.7±83	
Plasma Glucose	Yes	107.2±29.4	.04
(Fasting)	No	99.3±23.2	

observed in these subjects when compared on the basis of presence or absence of history of loud snoring in any first degree blood relative (Table 7,8). Neck circumference (p value .01), AHI value (p value .01)and fasting plasma glucose levels (p value .04) were found significantly higher in subjects with positive history of loud snoring in any first degree blood relative then in subject without history of loud snoring in any first degree blood relative (Table 9). Waist and hip circumferences were found marginally insignificantly (P value 0.07 and 0.08 respectively) higher in subjects with positive history of loud snoring in any first degree blood relative (Table 9).

DISCUSSION

In previous studies in several populations family aggregation of OSA has been shown.[11, 18 -21] In these studies, having a first degree relative with OSA increases the relative risk of OSA by the order of 1.5–2.0 and familial susceptibility to OSA increases directly with the number of affected relatives.[11, 22] In best of our knowledge, this is first such type of study in Indian population and first polysomnography based study in South Asian population. In our study Occurrence of family history of loud snoring in first degree blood relative was significantly higher in males. Similar results have shown in Sleep Heart Health Study where male gender was observed as an independent risk factor for OSA and has been found to increase the risk for moderate-to-severe OSA by nearly 1.6 times.[22] Mean value of neck circumference was found significantly large in subjects with positive family history of loud snoring in any first degree blood relative in comparison with negative history of loud snoring in any first degree blood relative. Mean values of waist circumference and hip circumference were also observed higher in subjects with positive history of loud snoring in any first degree blood relative. It is well established that obesity is closely associated with OSA and itself aggregates in families, so it is possible that familial aggregation of OSA is related to the genetics and phenotype of obesity as presented in our study setting. Craniofacial structures represent an additional mechanism by which genetics may affect the progression of OSA, the skeletal and soft tissue structures which are observed from generation to generation in different families.[22]

Difference in mean apnea hypopnea Index (AHI) values were also observed significantly higher in subjects with positive family history of loud snoring in any first degree blood relative in comparison with negative history of loud snoring in any first degree blood relative. This trend is very important and interesting since those subjects with positive family history of loud snoring in any first degree blood relative have marginally significant higher mean values of BMI (P=0.04) but they showed strongly significant differences in NC(P=0.01) and AHI (P=0.01) values In our study, fasting plasma glucose levels (p value .04) was found significantly higher in subjects with positive history of loud snoring in any first degree blood relative then in subject without history of loud snoring in any first degree blood relative. In previous studies both positive [23] and non-associated relation[24] was observed between OSA severity and Plasma glucose levels. Studies have shown that the prevalence of OSA is 78% in diabetic and 67% in pre-diabetics in comparison with those with normal glucose tolerance (33%).[25] and risk of developing type 2 DM increases with the severity of OSA.[26]

OSA is an independent risk factor for systemic hypertension.[27] Several studies have shown an increased prevalence of hypertension in patients with OSA.[28,29] Epidemiological studies have also shown an increased prevalence of coronary artery disease in OSA patients. Intermittent hypoxemia, sympathetic over-activation and simultaneous alterations in intra-thoracic, cardiac pressures during sleep, links OSA as a potential cause for cardiac ischemia. Studies have also shown an increase in the risk of acute myocardial infarction with increasing AHI.[30,31] In a study, OSA was also found independently associated with increased total cholesterol and LDL cholesterol levels, and carotid intima-media thickness irrespective of the cardiovascular co- morbidity.[32]

Thus, in spite of all scientific and clinical innovations about OSA in the last thirty years, majority of affected patients remain unnoticed and thus undiagnosed. The lack of an appropriate level of case suspicion and identification are partially driven by the fact that patients are frequently unaware of the associated symptoms that are often identified either by a bed partner or family member. Knowledge of potential risk factors for obstructive sleep apnea is therefore crucial to properly direct diagnostic attention at those with the highest risk. Early identification of high-risk individuals for occurrence of OSA may be key for preventing and or timely management of associated cardiovascular consequences in those subjects.

This study gives us a new direction for determining potential role of family history in near relatives in progression and occurrence of OSA in an individual. Further studies in this domain may reveal actual mechanism and phenotypic presentation of this risk factor in diseased population. This was a hospital based study so sampling and recruitment bias could not be completely eliminated in the setting. A community based study with appropriate sample size will serve the purpose.

REFERENCES

1. Yaggi HK, Strohl KP. Adult obstructive sleep apnea/hypopnea syndrome: Definitions, risk factors and pathogenesis. Clin Chest Med. 2010 ; 3:179-186.
2. Udwadia ZF, Doshi AV, Lonkar SG, Singh CI. Prevalence of sleep disordered breathing and sleep apnea in middle-aged urban Indian men. Am J Respir Crit Care Med 2004; 169:168-73.
3. Sharma SK, Kumpawat S, Banga A, Goel A. Prevalence and risk factors of obstructive sleep apnea syndrome in a population of Delhi, India. Chest 2006; 130:149-56.
4. Vijayan VK, Patial K. Prevalence of Obstructive sleep apnea syndrome in Delhi, India. Chest 2006: 130:92.
5. Suri JC, Sen MK, Adhikari T. Epidemiology of Sleep Disorders in the Adult Population of Delhi: A Questionnaire Based Study. Indian J Sleep Med 2008; 3:128-37.
6. Reddy EV, Kadhiravan T, Mishra HK,a Sreenivas V, Handa KK, Sinha S, et al. Prevalence and risk factors of obstructive sleep apnea among middle-aged urban Indians: a community-based study. Sleep Med 2009; 10:913-8.
7. Hunag SG, Li QY. Prevalence of obstructive sleep apnea-hypopnea syndrome in Chinese adults aged over 30 years in Shanghai. Zhongua Jie He He Hu Xi Za Zhi. 2003; 26:268-72.
8. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013 ;177(9):1006-14.
9. Lam JC, Sharma SK, Lam B. Obstructive sleep apnoea: definitions, epidemiology and natural history. Indian J Med Res. 2010 ; 131:165-70.
10. Al Lawati NM, Patel SR, Ayas NT. Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. Prog Cardiovasc Dis. 2009 ; 51:285-93.
11. Redline S, Tishler PV. The genetics of sleep apnea. Sleep Med Rev. 2000 ; 4:583-602.
12. Bell CG, Walley AJ, Froguel P. The genetics of human obesity.Nat Rev Genet. 200; 6:221-34.
13. Hussain SF, Cloonan YK, Islam M, Rahbar MH. Prevalence and associated risk factors of sleep-disordered breathing symptoms in young and middle-aged Pakistani employed adults. Sleep Breath. 2010;14(2):137-44.
14. Li KK, Kushida C, Powell NB, Riley RW, Guilleminault C. Obstructive sleep apnea syndrome: a comparison between Far-East Asian and white men. Laryngoscope 2000;110:1689–1693.
15. Teculescu D, Benamghar L, Hannhart B, Michaely JP. Habitual loud snoring. A study of prevalence and associations in 850 middle-aged French males. Respiration. 2006;73(1):68-72.
16. Bhatia M, Prasad K, Pande RN. Hindi version of epworth sleepiness scale: A validity study. The Indian J Sleep Med 2006 ;1(4) 171-174 ISSN 0973-340X.
17. Berry RB, Budhiraj R, Gottlieb DJ, Gozal D, Iber C, Kapur VK et al. Rules for scoring respiratory events in sleep: update 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012; 8:597-619
18. Redline S, Tishler PV, Tosteson TD, Williamson J, Kump K, Browner I *WWWW* The familial aggregation of obstructive sleep apnea. Am J Respir Crit Care Med 1995;151:682–687.
19. Mathur R, Douglas NJ. Family studies in patients with the sleep apnea hypopnea syndrome. Ann Intern Med 1995;122:174–178.
20. Pillar G, Lavie P. Assessment of the role of inheritance in sleep apnea syndrome. Am J Respir Crit Care Med 1995;151:688–691.
21. Gislason T, Johannsson JH, Haraldsson A, Olafsdottir BR, Jonsdottir H, Kong A, et al. Familial predisposition and cosegregation analysis of adult obstructive sleep apnea and the sudden infant death syndrome. Am J Respir Crit Care Med 2002;166:833–838.
22. Schwab RJ, Pasirstein M, Kaplan L, Pierson R, Mackley A, Hachadoorian R, et al. Family aggregation of upper airway soft tissue structures in normal subjects and patients with obstructive sleep apnea. Am J Respir Crit Care Med 2006; 173 : 453-63.
23. Kallianos A, Trakada G, Papaioannou T, Nikolopouloss I, Mitrakou A, Manios Eet al. Glucose and arterial blood pressure variability in Obstructive Sleep Apnea Syndrome. Eur Rev Med Pharmacol Sci. 2013 ;17(14):1932-7.
24. Sökücü SN, Karasulu L, Dalar L, Ozdemir C, Seyhan EC, Aydin S, *et al.* Effect of hypoxia on glucose metabolism in nondiabetic patients with obstructive sleep apnea syndrome. Arch Bronconeumol. 2013 ;49(8):321-5.
25. Fredheim JM, Rollheim J, Omland T, Hofsø D, Røislien J, Vegsgaard K, *et al.* Cardiovasc Diabetol.Type 2 diabetes and pre-diabetes are associated with obstructive sleep apnea in extremely obese subjects: a cross-sectional study.2011;10:84.
26. Wang X, Bi Y, Zhang Q, Pan F.Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies.Respirology. 2013 ;18(1):140-6
27. Grote L, Ploch T, Heitmann J, Knaack L, Penzel T, Peter JH. Sleep-related breathing disorder is an independent risk factor for systemic hypertension. Am J Respir Crit Care Med 1999;160:1875-82.
28. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010 ; 122:352-60.
29. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000; 342:1378-84.
30. Schäfer H, Koehler U, Ewig S, Hasper E, Tasci S, Lüderitz B. Obstructive sleep apnea as a risk marker in coronary artery disease. Cardiology. 1999;92(2):79-84.
31. Hung J., Whitford E.G., Parsons R.W., Hillman D.R.: Association of sleep apnea with myocardial infarction in men. Lancet 1990;336:261-64
32. Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM *et al.* Early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med 2005;172:613-8.