CENTRAL SLEEP APNEA IN ACROMEGALY *VERSUS* OBESITY

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INTRODUCTION: Sleep apnea syndrome is a common manifestation of acromegaly. Although the obstructive type of apnea was thought to be predominant there are some reports suggesting that central apneic episodes show a high rate and are related to abnormalities of central respiratory control.

AIM: The present study determines the presence and severity of central sleep apnea syndrome in patients with acromegaly compared with obese subjects.

MATERIALS AND METHODS: 35 consecutive acromegalic patients (min GH (growth hormone) during oral glucose tolerance test (OGTT) 6.6 ng/ml) and 19 obese subjects (BMI=44 kg/m^2) were polisomnographically recorded between 10 p.m and 6 a.m. Sleep and respiratory disturbances were manually staged according to standard criteria.

RESULTS: The prevalence of sleep apnea syndrome in acromegaly group was 45.7% (16 out of 35 patients). The median of minimum GH level during OGTT was 8.3 ng/ml in apnea group and 5.16 ng/ml in nonapneic group ($p>0.05$). In acromegaly group with severe sleep apnea syndrome central apnea rate was greater than 10% in 6 out of 7 subjects with REM sleep and in 7 out of 10 with NREM sleep whereas in obesity group this percent was present in 6 out of 18 (REM sleep), respectively 7 out of 19 (NREM sleep).

CONCLUSIONS: The study confirms the high prevalence of sleep apnea in acromegaly. GH serum level is not an indicator for the presence and severity of sleep apnea. Although the total time of central apnea per hour of sleep did not differ between the two groups, the percent (rate) of central apnea was significantly greater in acromegaly group.

Key words: acromegaly; obesity; sleep; apnea; respiration.

INTRODUCTION

Central sleep apnea (CSA) is a well-individualized subtype of sleep apnea episode characterized by concomitant loss of thoraco-abdominal respiratory effort

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and oro-nasal airflow. Central sleep apnea syndrome is traditionally associated with Pickwick syndrome, congestive heart failure and neuromuscular disorders.

The first observations that apneic episodes are frequently present during acromegalic patients sleep were made by Laroche (1), but associations between acromegaly and daytime sleepiness date 100 years earlier (2). Since then numerous studies confirmed the fact that sleep apnea syndrome (SAS) is a common manifestation of acromegaly (3-5). Large tongue, exceeding pharyngeal tissue and bone abnormalities were the anatomical elements used to explain an obstructive apnea type preponderance in this group of patients (6).

However, there are some reports concerning the fact that the central apneic episodes show "an unexpectedly high rate" (3) and are related to abnormalities of the central respiratory control (7) in acromegalic patients. Therefore, we decided to determine the presence of central sleep apnea syndrome in patients with acromegaly compared with obese subjects as the previous published studies lacked a control group.

MATERIALS AND METHODS

Patients. We investigated by polisomnography (PSG) 35 patients with acromegaly admitted consecutively in "Carol Davila" Endocrinology Department. Seven patients were recorded before any therapy, 12 patients underwent radiotherapy (mean time from radiotherapy 4.1 years), 9 transsfenoidal surgery and 7 complex treatment (surgery and radiotherapy) before polisomnographic recording. 3 patients were considered cured (min GH during oral glucose tolerance test was 0.7 ng/ml), the rest of patients still having active acromegaly (min GH during oral glucose tolerance test was more than 1 ng/ml). The control group was composed of 10 obese subjects with SAS diagnosed in the same department.

Study protocol. Each subject performed a complete PSG for diagnosis purpose according to the characteristics presented in fig. 1.

None of the subjects had stressful life events during the last two weeks, transmeridian flights and did not perform shift work. Administration of any drug affecting sleep or respiratory control was stopped and alcohol intake was within normal limits. All patients gave their informed consent.

Figure 1. Protocol of polisomnographic records.

Polisomnography. Full overnight polisomnography was performed using a computerized system (SleepScan II, Bio-logic System Corporation). Sleep staging was determined by monitoring with a 4-channel electroencephalography, a 2-channel electro-oculogram and mental electromyogram. Oro-nasal airflow was monitored by a 2-channel (oral and nasal) thermocouple. Thoraco-abdominal movements were recorded using respiratory effort bands. A lead II EKG recorded heart rhythm and a pulse-oxymeter recorded heart rate and oxygen saturation. Two electromyogram separate channels were used for leg movements.

Sleep was manually staged according to standard criteria (8). A central apnea was defined as an absence of oronasal airflow during sleep for >10 s associated with absent respiratory effort. Obstructive apnea was defined as cessation of oronasal airflow for >10 s in the presence of out-of-phase thoraco-abdominal effort. A hypopnea was defined as a more than 50% fall in oronasal airflow for >10 s with out-of-phase thoracoabdominal movement associated with a 4% fall in SpO_2 or an arousal. A mixed apnea was defined using the above criteria, when a central apnea included or terminated with obstructive components (9).

We considered that SAS is present in case of more than 5 respiratory events per hour of sleep. Severe SAS was defined as respiratory disturbance index > 30 events/hour (10).

Apart from the above described parameters we used a complex index, the total time of apnea during an hour of sleep. This index is obtained by multiplying the average number of events per hour of sleep (respiratory disturbance index, RDI) with average duration on event and it is expressed in seconds per hour of sleep. In our opinion it better describes the severity of sleep apnea syndrome because there are patients with low RDI but with very long apneic episodes.

Statistical analysis. All data were analyzed by a computer program (SPSS, version 10.0). To assess differences between patients with acromegaly and obesity, the Mann-Whitney U test and χ^2 were used.

RESULTS

The characteristics of patients are shown in Table 1. The median age of acromegaly group was similar to that of obesity group, but acromegalic patients with sleep apnea were significantly older than both obese and non-apneic acromegalic subjects. Body mass index was constant inside acromegaly group but differed statistically significant from obesity group. The severity of sleep apnea syndrome was similar in obese and acromegalic with severe sleep apnea subjects when we compared both the RDI and seconds of apnea per hour of sleep. Minimum GH level during OGTT did not differ between acromegalic subjects.

The prevalence of sleep apnea syndrome in acromegaly group was 45.7% (16 out of 35 patients). 10 patients (62.5% of apneic group, 38.6% of the whole

group) had a severe SAS confirmed by the presence of a RDI > 30 events/hour associated with troublesome clinical symptoms (somnolence, headache).

Table 1. Patients characteristics

	Acromegaly without SAS (n=19)	**Acromegaly with SAS (n=16)**	**Acromegaly with severe SAS (n=10)**	**Obesity (n=19)**
Age (years)	50 (42-56)	58 (54-63)	56.5 (54-64)[2]	45 (37-53)[1]
Sex ratio (F/M)	15/4	8/8	4/6	3/16
BMI (kg/m^2)	26.5 (23-29)	28 (25-31)	29 (27-33)	43 (40-47)[1]
Min GH during OGTT (ng/ml)	5.6 (1.3-14)	8.3 (5-11.5)	10 (6.5-13.6)	_
RDI (events/hour)	2.2 (0-4.4)	42 (13-55)	53 (47-65)[2]	65 (57-74)[1]
Seconds of apnea per hour of sleep	60 (18-75)	1014 (269-1622)	1501 (1083-2258)[2]	2150 (1621-2302)

All values are median (25, 75 percentile); 1 $p<0.05$ from acromegaly with severe SAS; 2 $p<0.05$ from acromegaly without SAS; BMI=body mass index; GH=growth hormone; OGTT=oral glucose tolerance test; SAS=sleep apnea syndrome; RDI= respiratory distress index.

Total time spent in apnea per hour of both REM and NREM sleep was similar in acromegalic patients with severe sleep apnea and obese patients. Also the time of different subtypes of apnea was similar between the two groups (Fig. 2 and 3).

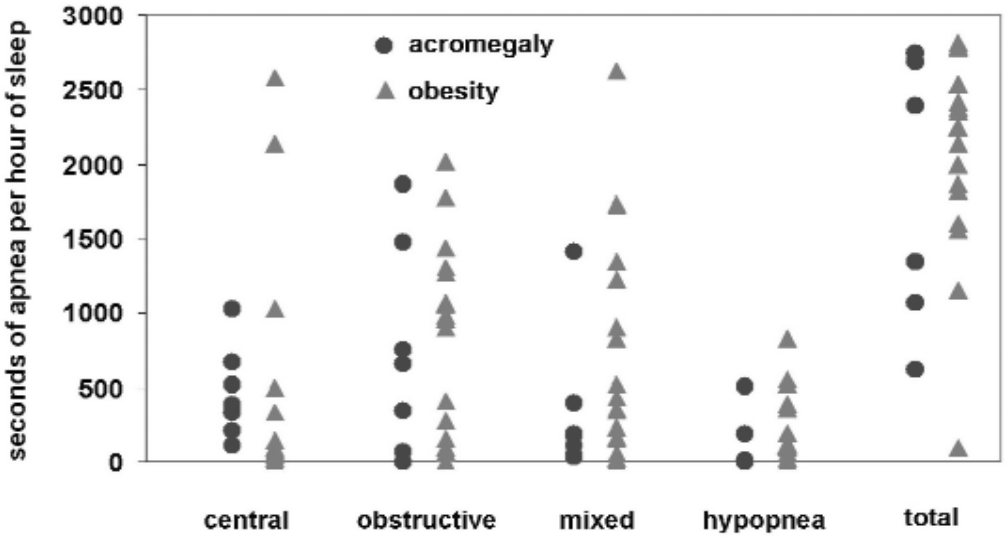

Figure 2. Duration of various subtypes of respiratory events during an hour of rapid eye movement (REM) sleep in acromegaly with severe SAS and obesity.One obese and 3 acromegalic subjects did not present REM sleep.

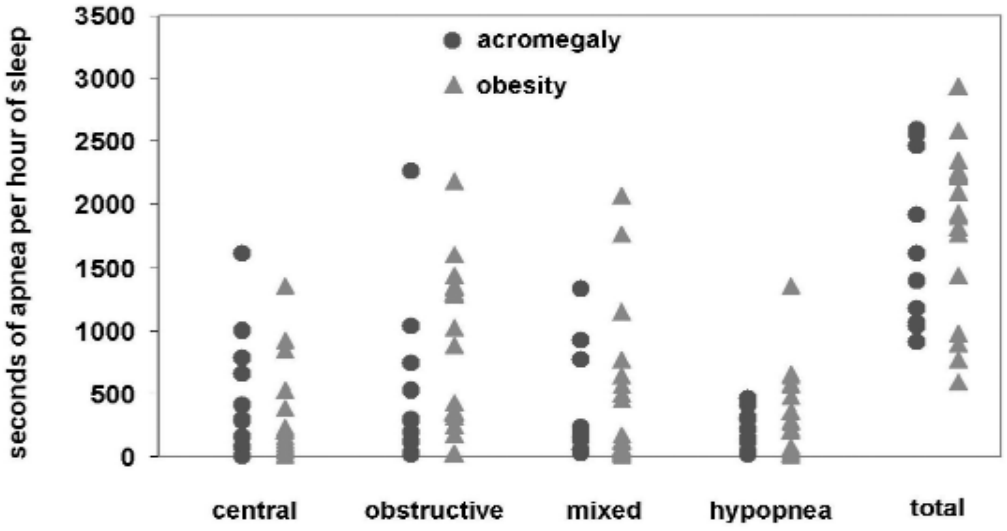

Figure 3. Duration of various subtypes of respiratory events during an hour of non-rapid eye movement (NREM) sleep in acromegaly with severe SAS and obesity.

The percent of central apnea time from total apnea time is shown in fig. 4A and 4B. It shows significant statistical differences, in both REM and NREM sleep, between obese and acromegalic patients. This means that although the effective time spent in central sleep apnea was similar more acromegalic subjects had a significant proportion of this sleep event.

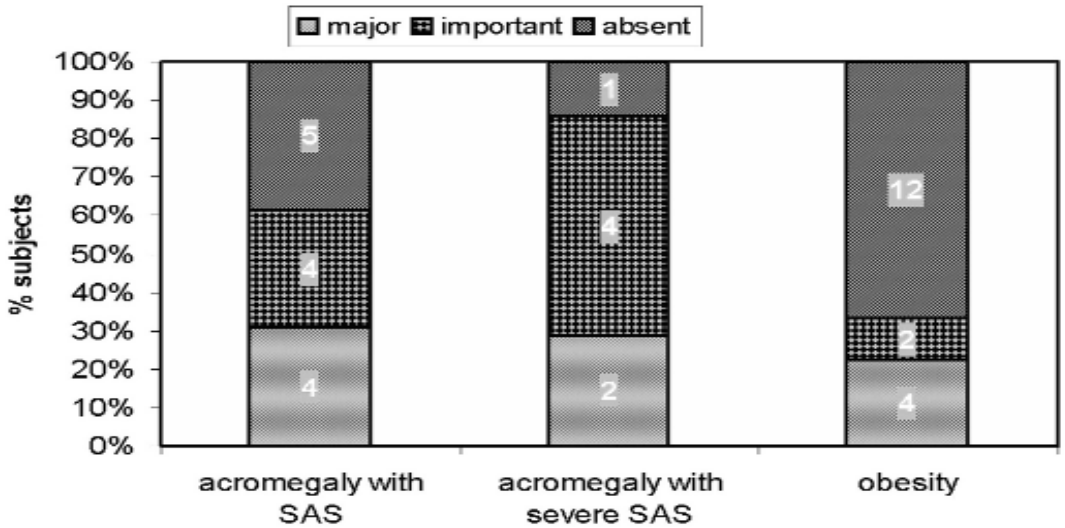

Figure 4A. Distribution of central sleep apnea during REM sleep. Values inside the bars represent number of cases. One obese and 3 acromegalic subjects did not present REM sleep. $p<0.05$ between obesity and acromegaly with severe SAS when major and important categories considered together. Major = predominant type of apnea (>50% of total apnea time), Important = >10% but not predominant, Absent = <10% of total time.

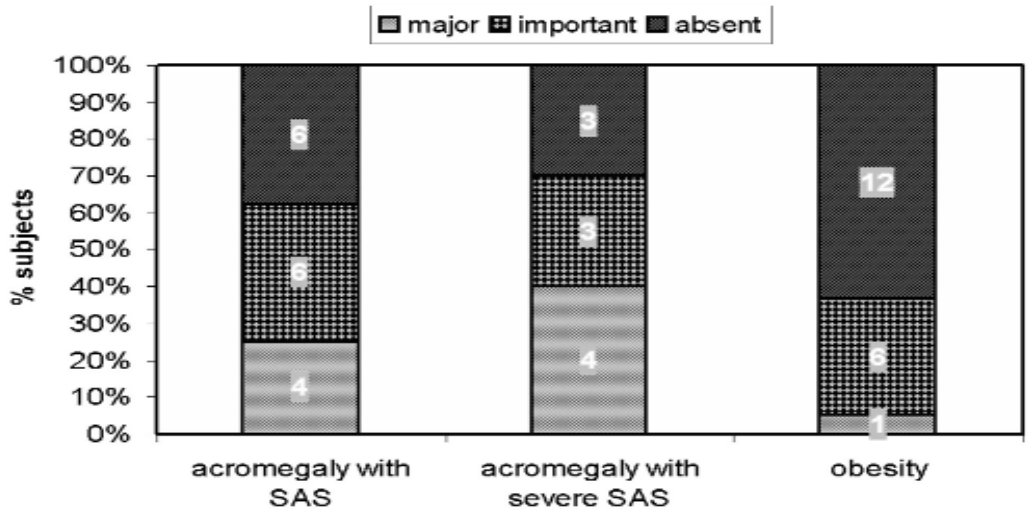

Figure 4B. Distribution of central sleep apnea during NREM sleep. Values inside the bars represent number of cases.p<0.05 between obesity and acromegaly with severe SAS when major and important categories considered together.
Major = predominant type of apnea (>50% of total apnea time), Important = >10% but not predominant, Absent = <10% of total time.

DISCUSSION

This study demonstrates that sleep apnea syndrome is a frequent complication of acromegaly. We found a 45.7% prevalence of SAS in our unselected, consecutive case series, which fits well with the prevalence reported by other authors. On a 53 patients series of whom 33 were referred because of clinical suspicion of sleep apnea, Grunstein (3) found a prevalence of 60%. In another large study regarding sleep apnea in acromegaly Rosenow and co-workers (5) studied 54 patients after excluding patients with known SAS and reported a prevalence of 39%. These studies also showed that sleep apnea was associated with increasing age and tended to be more common in males than in females, features also present in our group. The median age of apneic acromegalic patients was 58 years, statistically different from a 50 median of “normal breathers”. The men/women ratio was 8/8 with SAS vs 4/15 with no SAS.

The presence and importance of central sleep apnea in acromegaly is an unsolved issue. The morphological changes so characteristic of acromegaly stand for an obstructive type of apnea. Older studies used bony landmarks on plain lateral X-ray films to find anomalies that predispose to sleep apnea: dorsocaudal rotation of the mandible or narrowing of the nasopharynx (11-13). In addition there are lot of newer studies searching for soft tissue changes that confirmed macroglossia (14), swelling/collapse of pharyngeal walls (15) or a larger uvula (16).

On the other hand, however, there are papers pointing out to central sleep apnea as an important feature of SAS in acromegaly. Endoscopy performed during

apneic episodes revealed no posterior movement of the tongue (17). Grunstein reported a high rate of central (34% of patients with sleep apnea) (3) and speculated that increased central nervous system somatostatin (reactive to high levels of circulating GH) might be responsible for generation of these episodes (7). In this case the beneficial role of octreotide on sleep apnea remains controversed (14).

Our study confirms the presence of central sleep apnea episodes in the sleep of acromegalic patients. However, obese patients show also this kind of episodes and the seconds of central apnea per hour of sleep were similar between patients with the same severity of SAS. Moreover, other subtypes of nocturnal respiratory events acted in a similar fashion. On the other hand, the proportion or rate of central sleep apnea is greater in acromegaly (see figure 4). Six patients had a rate of apneas of central type greater than 10% in REM sleep, respectively seven in NREM sleep from the group of ten acromegalic patients with severe SAS, whereas there were 6 patients with important CSA in REM sleep and 7 in NREM sleep between 19 obese subjects. Differences are statistically significant.

There is a variety of both blood-borne and intracerebrally produced hormones that may account for predominance of central or obstructive type of apnea. The somatotropic axis, which is profoundly disturbed in acromegaly, is involved in intracerebral respiratory control. GH administration was shown to increase ventilatory drive in children with Prader-Willy syndrome (18) and high IGF-1 levels are thought to represent the main stimulus for hypercapnic ventilatory response recorded during wakefulness in acromegaly (19). On the other hand, somatostatin, which frequently shows high intracerebral levels in acromegaly, exerts a clear down-regulating effect on respiratory centers in medulla oblongata in new-born mice (20), rats (21) and humans (22).

Obesity, like acromegaly, is also charcterized by a disturbed central and peripheric hormonal array which may account for observed modified respiratory drive (23;24). Circulating leptin, an adipocyte-derived signaling factor, increases in accordance with body mass index (25), but the cerebrospinal fluid concentration can vary as much as fourfold between individuals (26). Leptin inhibits neuropeptide Y expression but stimulates CRH release (27). Since neuropeptide Y inhibits breathing (28) while CRH stimulates it (29), leptin may thereby influence on respiratory control. In obese mutant mice with leptin deficiency, leptin infusion increased ventilation during wakefulness and sleep, but particularly during rapid eye movement (REM) sleep (30). On the other hand, hyperleptinemia is related with hypercapnic respiratory failure. Obese hypercapnic patients have higher fasting serum leptin levels than eucapnic patients (31).

There is evidence implicating neuropeptide Y in human and animal obesity. Chronic central administration of NPY powerfully stimulates food intake in a variety of species and remarkable body weight gain (32-34). Although NPY seems to be an important orexigenic signal, NPY-null mice have normal body weight and adiposity (35) and human plasma or CSF levels of NPY do not differ from normal weight controls (36). In animals, neuropeptide Y has been linked with respiration.

Its administration decreases respiratory rate in rats (37) and neuropeptide Y-1 receptors mediates a decrease in ventilation in dogs (38). NPY role in human control of breathing has not been established yet.

CONCLUSIONS

This study confirms the high prevalence of sleep apnea in acromegaly. The predominant episode was of central type in acromegaly and of obstructive type in obesity. The hormonal milieu that determines the predominance of one or other type of apnea is not fully understood yet.

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