Sleep-Disordered Breathing (SDB) In Pituitary Adenomas: Preliminary Report.

GINEVRA DEL GIUDICE (✉ ginevradelgiudice@gmail.com)  
Hospital Gaetano Rummo: Azienda Ospedaliera Gaetano Rummo  
https://orcid.org/0000-0002-7643-7060

Itala Ventre  
Hospital Gaetano Rummo

Matteo De Notaris  
Hospital Gaetano Rummo

Giuseppe Catapano  
Hospital Gaetano Rummo

Mario Del Donno  
Hospital Gaetano Rummo: Azienda Ospedaliera Gaetano Rummo

Research

Keywords: Sleep-disordered breathing, obstructive sleep apnea, pituitary adenomas, GH deficiency, Polysomnography

Posted Date: February 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-137112/v1

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Abstract

Sleep-disordered breathing (SDB) and obstructive sleep apnea (OSA) are atypical presentation of pituitary adenomas secreting adrenocorticotropic hormone (ACTH) and growth hormone (GH). However, the non-secreting adenomas may cause alterations of sleep architecture.

Objective: The aim of the study was to evaluate clinical and sleep characteristics of OSA in a group of patients with functioning (FPA) and non-functioning pituitary adenomas (NFPA).

Methods: We analyzed 6 patients with SDB and pituitary adenoma during 3 years. SDB were studied by means of overnight polysomnographic study in our sleep lab.

Results: SDB were documented in 6 patients (3 M, mean age 50.8 years and mean BMI 35), with pituitary adenoma. In acromegalic patient was found a worsening of sleep parameters (AH index 18.4; AH index supine 29.6; OD index 12.7), successfully treated with CPAP therapy.

Conclusion: Our data show that in patients with pituitary adenoma, SDB should be better investigated. Expert consultation and a multidisciplinary approach to sleep disordered are needed in patients with pituitary adenoma.

Introduction

Pituitary tumors can manifest with signs and symptoms of pituitary hypofunction, hormone hypersecretion, or mass effect. The mass effect determine loss of pituitary hormones.

Functioning adenoma related with sleep disorders are mainly GH or ACTH-secreting.

Patients with GH deficiency have increased body fat and decreased lean body mass, and they might have decreased bone mineral density. Excess growth hormone (GH) before the fusion of the epiphyseal growth plates results in gigantism. The correlation between GH release and sleep pattern has been extensively studied in the last years and it is been demonstrated that GH secretion is reduced in OSA. In fact, GH itself may stimulate rapid eye movement (REM) sleep and it has been shown that in subjects with GH deficiency (GHD) sleep disorders and daytime sleepiness are frequent (1). Furthermore, hypothalamic GHRH have effects on sleep quality with a hypnotic activity and the ability to increase the duration and/or the intensity of deep non rapid eye movement sleep, i.e. slow-wave sleep (SWS), even in the absence of GH (2).

Polysomnographic studies indicate that as many as 33% of patients with Cushing’s disease have mild sleep apnea and 18% of patients have severe sleep apnea (3). Patients with Cushing’s disease also have decreased δ-sleep time and decreased δ-sleep-inducing peptide (4). Complaints of daytime sleepiness are therefore common.
In addition to the enlarged hands and feet characteristic of acromegalic patients also display hypertrophy of the facial bones, especially the mandible. Soft tissues of the nose, mouth, tongue, and lips become thicker and determined SDB. Thickening of the laryngeal and pharyngeal soft tissues (5) leading to a reduction in the size of the glottic opening, hypertrophy of the periepiglottic folds, calcinosis of the larynx (6), and recurrent laryngeal nerve injury can all contribute to airway obstruction and respiratory disease. An obstructive respiratory syndrome is observed in 25% of female and 70% of male patients (7). Obstructive sleep apnea (OSA) secondary to upper airway obstruction (8) can affect up to 70% of acromegalic patients; however, central respiratory depression of unknown etiology may also occur (9).

Our preliminary data have been collected to show the usefulness of the study of the DRS in patients with pituitary adenomas over 3 years.

**Material And Methods**

We recruited 6 patients with SDB and pituitary adenoma, admitted in our hospital from 2008 to 2011 yrs. Physical and anthropometric examinations were performed. BMI was calculated as weight (kilograms)/height2 (square meters). Epworth Sleepiness Scale (ESS) and Berlin questionnaire modified, has been used to diagnose daytime sleepiness and sleep disorders symptoms.

All patients were studied with pulmonary function tests including arterial blood gas analysis, spirometry, Body Plethysmography and 6-minute walk test. *(see Table 1)*

SDB were studied by means of overnight polysomnographic study in our sleep lab (Weinmann’s sleep lab system SOMNOLab). Each subject had overnight polysomnography (PSG) for evaluation of sleep abnormalities, supervised by trained sleep technologists in the sleep medicine laboratory. Every PSG was performed in a quiet, darkened room, without the use of sleep-inducing medications, and was interpreted by a single sleep medicine physician.

The scoring criteria were according to event definition by American Academy of Sleep Medicine (AASM) manual (15). A standard overnight PSG included a 4-lead electroencephalogram (C3, C4, O1, and O2), two bilateral electrooculogram leads referenced to A1 or A2, and one submental and two tibial electromyograms. Respiratory measurements included chest wall and abdominal movement using inductance pneumography; airflow using a nasal cannula connected to a nasal pressure airflow; oxygen saturation (SaO2). Video and audio recordings were obtained for each study. Sleep architecture was assessed by standard techniques (25). Information obtained from each PSG included sleep onset latency (SOL) and rapid eye movement sleep (REM)-onset latency, TST, sleep efficiency, time spent in each sleep stage (minutes and percentage), and the number of arousals. Recorded respiratory data included counts and indices of the following events: obstructive apneas and hypopneas (OAHI), central apneas [central apnea index (CAI)], and mixed apneas recorded in non-REM (NREM) sleep, REM sleep, and total sleep.

Every patient was analyzed in Department of Internal Medicine section of endocrinology. All patients performed a magnetic resonance imaging (MRI). Blood samples were obtained for serum IGF-I, fT3, fT4,
TSH, LH, FSH, testosterone (estradiol in fertile females during follicular phase), PRL, ACTH and cortisol. In each patient we performed a basal study of thyroid, adrenal and gonadal - pituitary axis and a dynamic evaluation. Deficit of GH (GHD) were diagnosed with GH-releasing hormone (GHRH) plus arginine stimulation test. Cushing syndrome (CS) was diagnosed with measurement of urinary cortisol in a low-dose dexamethasone (1 mg) suppression test (Nugent Test), IGF-1 and growth hormone levels and measurement of GH during OGGTT (oral glucose tolerance test). All patients except one (not operated for medical reasons) underwent standard 3D endoscopic endonasal trans-sphenoidal surgery in our Neurosurgical Department. Before surgery, they had a complete clinical, endocrinological, and visual field evaluation. The preoperative imaging studies were performed using an MRI with and without intravenous gadolinium contrast and CT scan of the sellar region. All patients had complete removal of the lesions assessed by a postoperative MRI.

**Results**

SDB were documented in 6 patients (3 M, mean age 50.8 years), with pituitary adenoma.

Three NFPA, two patients with FPA and one with acromegaly, were diagnosed after neurosurgery resection (see table 2).

Mean Oxygen desaturation at rest was 96 ± 2%. Mean BMI 35. ESS mean reported were 10, mean SaO2 was 93 ± 5% and AH index were 6.7 ± 1.7, with a prevalence of obstructive events. Oxygen desaturation index (ODI) was 7.8 ± 1.2, REM sleep duration (mean) was 15.4 ± 6.8% of total sleep time and SWS (mean) was 22.4 ± 11.1% (see table 3).

The Epworth Sleepiness Scale score was equal to or greater than 10 in ACTH-PA and GH-PA (ESS mean value 10.5).

In acromegalic patient (Fig. 1), was found a worsening of sleep parameters compared to other patients (AH index 18.4; AH index supine 29.6; OD index 12.7) successfully treated with CPAP therapy.

**Discussion**

Our data showed that patients with pituitary adenoma can benefit when the study of SDB is performed. Patients with PA can also benefit from the use of CPAP, even in mild OSA associated with a high ESS score.

Although the patients with NFPA and Cushing's syndrome were affected by a mild OSA, they reported daytime sleepiness, snoring and difficulty falling asleep.

To better understand the relationship between cortisol levels and OSAS, several studies have evaluated the effects of the use of CPAP on serum cortisol. Although some authors have reported that CPAP does not influence cortisol, conversely Vgontzas and coll. have demonstrated that sleep apnea in obese
patients is associated with a mild but significant at-night elevation of cortisol levels, compared with nonapneic obese controls, which is corrected after the use of CPAP for 3 months. The decrease of cortisol levels after CPAP use may be related to the elimination of the stress of repetitive apnea and sleep fragmentation and/or better oxygen saturation (11). Obstructive sleep apnea syndrome is characterized by changes in the serum levels or secretory patterns of several hormones, the hypothalamic-pituitary-adrenal (HPA) axis and sleep interact in multiple ways in sleep architecture. In patients with OSAS an alteration of hypothalamic-pituitary-adrenal axis has been well described. Sleep fragmentation, due to repetitive apnoeas, may increase the plasma catecholamine as well as Corticotropin Releasing Hormone (CRH) and cortisol levels. Activation of HPA axis seems to be a risk factor for the development of metabolic syndrome in OSAS patients. The visceral obesity and insulin resistance conduct to metabolic syndrome and consequently to sleep apnea which in turn, with elevated nocturnal cortisol and insulin levels, may contribute to and accelerate the worsening of visceral obesity and the metabolic syndrome (10). It is also useful to remember that hypoxia induced by apnea is a stressful condition and it has per se been shown to induce activation of HPA axis both in animal models (12) and in patients with OSAS (13).

**Conclusions**

SDB in patients with functioning and non-functioning pituitary adenoma are underdiagnosed. Evaluation of sleep disorders is not included among the preoperative and postoperative exams in subjects with DRS.

Expert consultation and a multidisciplinary approach to sleep disordered are needed in patients with pituitary adenoma. In fact, only the interaction between chest physician, endocrinologist, neurosurgeon and radiologist makes a correct diagnosis and treatment.

The major limitation of this study is that it is retrospective.

**Abbreviations**

Sleep-Disordered Breathing (SDB)

Obstructive Sleep Apnea (OSA)

Polysomnography (PSG)

Functioning Pituitary Adenomas (FPA)

Non-Functioning Pituitary Adenomas (NFPA)

Epworth Sleepiness Scale (ESS)

Growth Hormone (GH)

GH Deficiency (GHD)
Rapid Eye Movement (REM)

Declarations

**Ethics approval and consent to participate** Not applicable

**Consent to publication:** Written informed consent was obtained from the patient for the publication of clinical data and any images. A copy of the written consent is available for review by the editor of this journal.

**Availability of data and material:** Our data are available in the data archive of the Pneumology department of the Rummo hospital

**Competing interests:** The authors declare that they have no competing interests.

**Funding:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported.

**Authors' contributions:** All authors contributed equally to the writing of the manuscript. All authors have read and approved the final manuscript. All authors read and approved the final manuscript.

**Acknowledgements:** Not applicable

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Tables

Due to technical limitations, table 1,2,3 is only available as a download in the Supplemental Files section.

Figures
Acromegalic patient in our Sleep Lab

**Supplementary Files**

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- table.doc