THE STUDY ON RELATIONSHIP BETWEEN OBSTRUCTIVE SLEEP APNEA, GASTROESOPHAGEAL REFLUX DISEASE AND DAYTIME SOMNOLENCE

THESES

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INTRODUCTION

The introduction of this paper gives a short summary of connection between obstructive sleep apnea and gastroesophageal reflux disease as well as relationship between gastroesophageal reflux disease and daytime somnolence.

This paper consists of two clinical studies.

There is an increasing mass of evidence for a link between the Obstructive Sleep Apnea (OSA) and Gastroesophageal Reflux Disease (GERD). The large negative intrapleural pressure swings during apnea should facilitate reflux-event. A further factor to be considered regarding the OSA-GERD relationship is that the diaphragm is connected to LES through the phreno-esophageal ligament (PEL). During apnea the respiratory work of the diaphragm increases extremely. This increased burden affects the cardia through the frequent change of the position of PEL. This leads partly to the loss of the cardia muscle tone. Significantly more reflux events could be identified for OSA patients relative to the controls during one-channel esophageal pH-metry. The number of reflux events could be reduced with nasal Continuous Positive Airway Pressure (nCPAP) treatment for both the patients with OSA and GERD. These data suggest that OSA may be a significant cause of GERD. The influence of severity of OSA on endoscopic findings in patients with GERD and OSA has not been analyzed yet. We have also investigated the intensity of snoring and its relation to the endoscopic severity of GERD in primary snorers.
On the other hand, the investigations focusing on the relationship between sleep related breathing disorders and GERD have indicated the adverse effect of nocturnal reflux events on the sleep structure. Partly, sleep is potentially conducive to the gastro-esophageal reflux events. The physiological antireflux mechanisms – swallowing rate, salivation, the pressure of the upper esophageal sphincter, gastric emptying - are reduced as well as the „heartburn-signal” is depressed during the state of sleep. Studies of parallel 24 hour pH-metry and polysomnography amongst obstructive sleep apneic patients showed that some reflux events coincide with arousals. In 2003 the ProGERD study has established that the effective treatment of GERD reduces sleep disturbances. The results of a Gallup Telephone Survey – conducted on behalf of the American Gastroenterological Association – have shown that the nocturnal heartburn and the regurgitation of gastric content caused frequent awakenings and sleep disturbances, which could affect daytime performance and the quality of life. The influence of GERD on daytime cognitive functions has not been analyzed yet. In this study we focus on one of the important cognitive functions, on daytime sleepiness and its relation to the severity of GERD.
AIMS

The aims of this study were follows:

1. To assess the relationship between endoscopic severity of GERD and apnea-hypopnea index as an indicator of severity of OSA. To assess endoscopic severity of GERD and its relation to intensity of snoring in patient with primary snoring. Compare these populations in respect of clinical parameters and frequency of typical reflux symptoms.

2. To assess the relationship between endoscopic severity of GERD and Epworth sleepiness scale as an indicator of daytime somnolence in GERD patients.

PATIENTS AND METHODS

1. 57 patients with proven obstructive sleep apnea and 25 patients with primary snoring were investigated. In all cases a 12-channel polysomnography, (2-channel EEG/electroencephalography/, EOG /electrooculography/, chinEMG/electromyography/, ECG/electrocardiography/, nasal and oral airflow-metry, detection for O2-saturation, pulseoxymetry, detection for thoracic and abdominal movements, phonometry for measuring of quantity and intensity of snoring) were performed using Morpheus Medatech System. All patients underwent upper panendoscopy and were asked about frequency of typical reflux symptoms (heartburn, regurgitation of gastric
content, dysphagia – positive was: two symptoms, at least three times a week). Epworth Sleepiness Scale (ESS) was completed by patients to measure their daytime sleepiness. The classification of GERD was based on endoscopic findings. We used the conventional Savary-Miller classification of the disease. The value of apnea-hypopnea index (AHI) was measured in Morpheus Medatech system by decrease or stop of oro-nasal airflow. We classified the severity of OSA according to recommendation of American Academy of Sleep Medicine (AHI: 5-14 mild, 15-30 moderate, >30 severe). Primary snoring was diagnosed: duration of snoring longer than 15% of sleep period and AHI<5.

2. 134 patients underwent an upper panendoscopy as indicated by the typical reflux symptoms and were also investigated with regard to daytime somnolence. Sleepiness was evaluated by Epworth Sleepiness Scale, which was compared to the severity of endoscopic findings (Savary-Miller). Patients with psychiatric disorders or being on sedato-hypnotics as well as shift workers were excluded from the study.

Statistical methods

The patient data were collated on an Excel 9.0 worksheet, including the severity grades of GERD (0-4), the Apnea-Hypopnea Index (AHI), the frequency of typical GERD, snoring intensity, age, gender, the score of Epworth Sleepines Scale and Body Mass Index (BMI). We used the SPSS 9 for Windows software package for the statistical procedures.
In case of continuous and category variables a nonparametric T-test (Mann-Whitney), one-way ANOVA-test and chi-square-test were used. In the event of dichotomous variables chi-square „for trend”-test were performed. The relationship between the severity of the reflux disease and apnea-hypopnea index was analyzed with the help of logistic regression analysis. We relied on the conventional p<0.05 critical values regarding the statistical tests of the results.

The extent and statistical strength of the potential relationship between GERD severity and daytime somnolence was captured by estimating the impact of diagnosed GERD categories on the indicators of sleepiness relative to the two endpoints of the reflux disease severity scale. We relied on the conventional p<0.05 critical values regarding the statistical tests of the results. At the same time, we also took into account a somewhat weaker, 10% significance level when evaluating the observed associations, given the relatively small size of the available sample.

**RESULTS**

**Study on OSA-GERD-snoring connection:**

The available population covered 57 OSA patients. This population was characterized by an average age of 51.38 years (SD±9.16), a male/female ratio of 2.8:1 (73.7% vs. 26.3%) and an average BMI of 34.20 kg/m² (SD±8.79). Using the Savary-Miller definitions, our patients
displayed the following distribution alongside the endoscopic categorization of reflux disease: 11 (19.3%) GERD 0 subjects, 13 (22.8%) GERD I subjects, 20 (35.1%) GERD II subjects, 7 (12.3%) GERD III subjects, and 6 (10.5%) GERD IV subjects. The population mean of AHI used as a direct measure of severity of sleep apnea here was 40.8 (SD±35.18). The patients were divided into two groups according to the severity of the sleep apnea: “mild-moderate” („A”') – apnea-hypopnea index = 5-30, n=27 and „severe” („B”) - apnea-hypopnea index >30, n=30. The percentage of female patients was 37% in the group „A” and 16% in „B”. The BMI was significantly higher in the group „B” than in „A” (p=0.0002). There was not significant difference between groups in respect of typical reflux symptoms (52% vs.47%) but in 49.5% of the study population these symptoms were “poor” according to our determination. Analyzing the endoscopic findings of GERD a higher frequency of severe cases was found in the group „B” (p=0.0001). In the group „A” the percentage of GERD 0 was one third of cases, whereas in the group „B” that was only 7%. We compared clinical (sleep) parameters and GER-related symptoms in each grade of GERD. No significant differences were found between grades in respect of age, gender and the frequency of GER-related symptoms. A positive correlation could be found between severity of GERD and BMI (p=0.04). A very close connection has been demonstrated between severity of GERD and AHI-value (p=0.0001) and the score of Epworth-scale (p=0.0006). We could reach essentially similar conclusions on the basis of logistic regressions investigating the severity of endoscopic findings and AHI-
values as indicator of severity of OSA. This model has shown that in case of high AHI the chance of presence of severe GERD is 4.09 fold. The weak connection between BMI and severity of GERD was not significant in this model.

Primary snorers - 25 patients - was characterized by an average age of 50 years (SD±11.08), an average BMI of 28.42 kg/m² (SD±5.45) and a male/female ratio was 52%/48%. The severity of GERD, age, gender and the sleep parameters were compared to the OSA group. There was not significant difference between groups in respect of age and gender. The mean of BMI was significantly higher in OSA group (p=0.0002). Analyzing the endoscopic findings of GERD a significantly higher frequency of severe cases was found in the OSA group compared to the snorers (p=0.006). We did not find significant difference in respect of typical GERD symptoms (p=0.96). However, in the snorer group the occurrence of these symptoms significantly connected with severity of GERD in contrast to the OSA patients (p=0.0015). We have also established a positive and significant correlation between endoscopic severity of GERD and intensity of snoring (p=0.006).

**Study on relationship between GERD and daytime somnolence:**
The total available population covered 134 patients, which were characterized by an average age of 52.9 years (SD±16.7), a male/female ratio of 65: 69, and an average BMI of 26.4 (SD±5.1). Using the Savary-Miller definitions our patients displayed the following
distribution alongside the endoscopic categorization of reflux disease: 24 (18.9 %) GERD 0 subjects, 29 (21.6%) GERD I subjects, 56 (41.8%) GERD II subjects, 13 (9.7%) GERD III subjects, and 12 (8.9%) GERD IV subjects. The population means of the Epworth sleepiness scale used as a direct measure of somnolence here was 7.6 (SD±4.3) covering the GERD 0-IV patients. The “abnormal Epworth” took the frequency of 44.8 %. Note that we included only the sample of GERD 0-III cases with 122 patients into the detailed statistical analysis. The exclusion of GERD IV group was justified on the basis of the consideration that this set of patients is inherently heterogeneous regarding the anatomic abnormalities as well as the clinical severity of the reflux disease itself.

The “abnormal Epworth” took the frequency of 44.3 %. The population means of the Epworth sleepiness scale was 7.4 (SD±4.2). The means for the Epworth indices exhibited increasing values alongside the severity of GERD taking the sub-groups of GERD 0 and GERD I-III together. Whereas GERD I exceeded by 0.5 (6.2% of the population average) and GERD II by 0.7 (9.2% of the population average) the 6.7 mean value of our GERD 0 cluster, this difference was already 4.1 (54.5% of the population average) in the case of the GERD III group. This increasing tendency reflecting the severity of GERD appeared to be even more characteristic with respect to the frequencies of “abnormal Epworth”. This increasing tendency reflecting the severity of GERD appeared to be even more characteristic with respect to the frequencies of “abnormal Epworth”. Compared with the 29.1% ratio calculated for GERD 0, the observed percentage
increments in the presence of hypersomnia were: 8.8% (19.7% of the population average) for GERD I, 17.3% (38.7% of the population average) for GERD II, and 47.8% (106.9% of the population average) for the GERD III group. To evaluate our observations indicating a positive association between severity of GERD and daytime somnolence more precisely, we performed linear regressions for the variation of the Epworth index and logistic regressions for the probability of “abnormal Epworth” over the sample comprising the GERD 0-III cases. Apart from the categorical variables constructed for the reflux disease classifications, we also included the BMI values, and the observations for gender and age as explanatory variables. As far as the estimates for the GERD categories were concerned, the multivariate regression seemed to support the direct observation that reflux disease severity incurs a positive effect on the extent of the Epworth index. In numeric terms, this implied that after filtering out the joint effect of the control variables the Epworth index was estimated to be lifted up by 47.5% of the population mean relative to GERD 0 in the case of GERD III. At the same time, the corresponding t-values confirmed our previous results indicating that GERD III was associated with a significantly greater sleepiness scale relative to GERD 0, while GERD 0, GERD I and GERD II were associated with a significantly smaller one relative to the GERD III group. We could reach essentially similar conclusions on the basis of the logistic regressions investigating the occurrences of the “abnormal Epworth”. The estimates relative to GERD 0 gave again increasing coefficients with odds ratios greater than one. The odds ratio
computed for GERD III was different from one at p<0.05. Correspondingly, we found in absolute terms that the estimated ratio of hypersomnia to the normal cases ceteris paribus increased by 7.4 times in the GERD III group compared with the least severe reflux disease cluster. The Wald-tests performed on these coefficients indicated again that the probability of hypersomnia to occur was significantly higher for GERD III relative to GERD 0, and significantly lower for GERD 0, GERD I and GERD II relative to GERD III.

**SUMMARY**

Characteristics of our OSA population were consistent with literature data namely the patients were overweight with male in the majority. The snorer group was similar in respect of age and gender, but the mean of BMI was significantly lower than in OSA group. We found a positive correlation between body mass index and the degree of severity of OSA (p=0.0002), which is also consistent with literature data. A close connection has been demonstrated between severity of GERD and the score of Epworth-scale as an indicator of daytime somnolence in patients with OSA (p=0.006). There was no difference between the two groups in regard of typical symptoms’ occurrence, but these symptoms were poor in half (50.5 %) of all patients. However, in the snorer group the occurrence of these symptoms significantly connected with severity of GERD in contrast to the OSA patients (p=0.0015). A high frequency of reflux esophagitis was found (? 80%) in OSA patients.
compared to the general population (40-60%) and primary snorers (44%). A close connection has been demonstrated between severity of GERD and AHI-value (p=0.0001) as an indicator of severity of OSA. We could reach similar conclusions on the basis of logistic regressions investigating the severity of endoscopic findings and AHI-values. This model has shown that in case of high AHI the chance of presence of severe GERD is 4.09 fold. The weak connection between BMI and severity of GERD was not significant in this model. We have established a positive correlation between endoscopic severity of GERD and intensity of snoring (p=0.006).

In this study we focused on one of the important cognitive functions, on daytime sleepiness and its relation to the severity of GERD. Daytime sleepiness was chosen to relate the severity of GERD assessed by panendoscopy to the measure of ESS. Our results indicate that the more severe GERD groups categorized by the Savary-Miller classification exhibit a gradually increasing, more „somnolent” result by the ESS. Moreover, while in the group GERD 0 only 29% of patients reached the mild somnolence value of 8 on ESS, in GERD I this rate grows up to 39% and in GERD II it reaches 46%. In the group of GERD III more than 77% of the subjects suffered of significant somnolence. This relationship was confirmed by the multivariate regression analysis when estimating the ESS result directly as well as when examining the probability of at least mild hypersomnia, especially with regard to significantly higher somnolence observed in the most severe GERD
population. Our findings seem to imply that there is a significant fragmentation in the sleep structure in the case of severe GERD. Previous investigations already indicated that arousals, which play a major role in the fragmentation of the sleep structure, could be generated by some reflux events. The higher positioned and longer than 5 minutes reflux events are more likely to cause arousals. If the reflux content leaves the esophagus and migrates into the upper respiratory tract, it could irritate the acid sensitive receptors, which are located in the mucus layer. This irritation would lead to the change in muscle tone as a manifestation of arousal producing a motor restless sleep. In addition, the regurgitation of the acidic gastric fluid may cause discomfort, choking, aspiration, and disturbed sleep with multiple awakenings. It is important to explore daytime somnolence in the cases of severe and therapy refractory GERD. These cases can be caused by sleep-related breathing disorders, which can augment the symptoms of GERD and cause daytime sleepiness as well.
NEW SCIENTIFIC RESULTS

1. A high frequency of reflux esophagitis was found (80%) in OSA patients compared to the general population (40-60%) and primary snorers (44%).

2. We have verified a positive and significant correlation between AHI-value as an indicator of severity of OSA and endoscopic findings of GERD with different statistical methods in patients with OSA and established that more severe OSA is accompanied by more severe GERD.

3. We have established a positive and significant correlation between endoscopic severity of GERD and intensity of snoring in primary snorers.

4. A positive and significant correlation was found between endoscopic severity of GERD and daytime somnolence. Our results indicated that severity of Gastroesophageal Reflux Disease influences daytime somnolence.
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