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• CLINICAL RESEARCH •

Severity of gastroesophageal reflux disease influences daytime somnolence: A clinical study of 134 patients underwent upper panendoscopy

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Abstract

AIM: To asses the relationship between severity of gastroesophageal refluxe disease and Epworth sleepiness scale as an indicator of daytime somnolence.

METHODS: One hundred and thirty-four patients underwent an upper panendoscopy as indicated by the typical reflux symptoms and were also investigated with regard to somnolence. Sleepiness was evaluated by Epworth Sleepiness Scale, which was compared to the severity of endoscopic findings (Savary-Miller/modified by Siewert). Patients with psychiatric disorders or being on sedato-hypnotics as well as shift workers were excluded from the study. The relationship between the severity of the reflux disease and daytime somnolence was analyzed with the help of multivariate regression analysis.

RESULTS: A positive tendency was found between the severity of the reflux disease and the corresponding Epworth Sleepiness Scale. In the case of the more severe type - Savary-Miller III - at least a mild hypersomnia was found. For this group daytime somnolence was significantly higher than in the case of the non-erosive type of Gastroesophageal Reflux Disease representing the mildest stage of reflux disease.

CONCLUSION: The severity of Gastroesophageal Reflux Disease influences daytime somnolence.

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INTRODUCTION

Sleep is potentially conducive to the gastro-esophageal reflux events. The physiological antireflux mechanisms – swallowing rate, salivation, the pressure of the upper and the lower esophageal sphincter, gastric emptying - are reduced as well as the the "heartburn-signal" is depressed during the state of sleep[1-6]. Moreover, the typical lying position facilitates the flow of the gastric content towards the esophagus due to the forces of gravitation[2]. Studies of parallel 24 h pH-metry and polysomnography amongst obstructive sleep apneic patients showed that some reflux events coincide with arousals[3]. At the same time, it was also found that some apneic periods contribute to considerable reflux events, while others not. On the other hand, earlier investigations focusing on the relationship between sleep related breathing disorders and Gastroesophageal Reflux Disease (GERD) have indicated the adverse effect of nocturnal reflux events on the sleep structure[4,5]. In this respect some epidemiological studies have suggested a relationship between GERD and daytime sleepiness[6-9]. In 2003 the ProGERD study has established that the effective treatment of GERD reduces sleep disturbances[10]. 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[11]. Therefore it appears that the nighttime reflux could have a considerable impact on the quality of sleep and it can also play a significant role in the developing of restless sleep experienced widely by the patients.

The influence of GERD on daytime cognitive functions has not been analyzed yet. In this study we focused on one of the important cognitive functions, on daytime sleepiness and its relation to the severity of GERD. The aim of the study was to describe the association between the severity of GERD and daytime somnolence.

MATERIALS AND METHODS

The database

The study was conducted by a gastroenterologist in two centers. The patients were referred for upper panendoscopy with the typical symptoms of GERD untreated. Psychiatric patients or those who took sedato-hypnotics and shift workers were excluded. The classification of GERD was based on endoscopic findings and the severity of the esophagitis[12]. We used the conventional Savary-Miller classification of the disease modified by Siewert. The Epworth Sleepiness Scale (ESS) was used as an indicator of daytime somnolence, which is a simple questionnaire measure to asses daytime somnolence amongst patients suffering of sleep-awake disorders[13-15]. The patient data were collated on an Excel 9.0 worksheet, including the severity grades of GERD (0-IV), the Epworth scale (0-24), age, gender and Body Mass Index (BMI).

Statistical methods

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. We used the *SPSS 9*-software package for the statistical procedures.

RESULTS

Basic descriptions of the study population

The total available population covered 134 patients the descriptive statistics are given in Table 1. This population was characterized by an average age of 52.9 years (std. dev. 16.7), a male/female ratio of 65: 69, and an average BMI of 26.4 (std. dev. 5.1). Using the Savary-Miller definitions as modified by Sievert, 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. Note that we included only the sample of GERD 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 severity of the reflux disease itself. Obviously, this could be a confounding factor in relation to the effect on our analyzed dependent variable, the daytime sleepiness.

Table 1 Descriptive statistics of the total study population

Variable	Minimum	Maximum	Mean	SD
Age (yr)	17.00	83.00	52.940	16.752
Male	0	1	0.485	-
BMI	17.54	43.94	26.420	5.133
GERD 0	0	1	0.179	-
GERD I	0	1	0.216	-
GERD II	0	1	0.418	-
GERD III	0	1	0.097	-
GERD IV	0	1	0.089	-
EPWORTH	1.00	24.00	7.440	4.226
		n=134		

Note: The mean values of the dichotomous variables (with cases taking values 0 or 1) refer to frequencies and thus the standard deviation is not an applicable measure for them.

The population means of the Epworth sleepiness scale used as a direct measure of somnolence here was 7.4 (SD. 4.2) (while slightly higher -7.6 (SD4.3) – for the sample covering the GERD 0 and GERD I-IV patients). We created a further dependent variable, "abnormal Epworth", for the observations with an index value greater than 8 taking into account that at least a mild form of hypersomnia could be diagnosed above this level. Since our sample was not primarily directed at patients suffering from sleep disorders, it did not seem to be reasonable to select a higher limit. Nevertheless, the detectable tendencies did not differ qualitatively for the critical Epworth value of 10 from the one, which is presented here. The "abnormal Epworth" took the frequency of 44.8% (and 44.3% after dropping the GERD IV group).

Table 2 shows the patterns for the two above described dependent variables by GERD diagnosis. It is evident that 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". 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. For information, the table gives our observations for the GERD IV patients as well: we found the lowest group mean value with respect the Epworth index, but the occurrence of hypersomnia went above the population average. This seems to provide a further aspect regarding the heterogeneity of patients diagnosed with GERD IV.

Table 2 Measures of daytime somnolence by GERD groups

GERD	*n*	EPWORTH index Mean (Std. dev.)	"Abnormal" EPWORTH >8 Frequency
GERD 0	24	6.708 (4.639)	0.291
GERD I	29	7.172 (4.036)	0.379
GERD II	56	7.393 (3.706)	0.464
GERD III	13	10.769 (5.890)	0.769
GERD IV	12	6.166 (2.588)	0.500
Total sample	134	7.440 (4.226)	0.447

Notes: 1. The equality of the mean values for the Epworth indices could be rejected at 5% significance level on the basis of the Student *t*-tests for the following pairs of GERD groups: GERD III *vs* GERD II, GERD III *vs* GERD I, GERD III *vs* GERD 0, and GERD III *vs* GERD IV. 2. The Pearson chi-square tests for the frequencies of "abnormal" Epworth indices indicated significant differences at 5% critical value in the case of the following 2x2 tables : GERD III *vs* GERD II, GERD III *vs* GERD I, GERD III *vs* GERD 0.

Statistical analysis and results

To evaluate our observations indicating a positive association between severity of GERD and 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 and GERD I-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. Since our estimated models typically gave a better overall fit when measuring age above 50 rather than the number of years directly, we present our result with the former control variable below.

Table 3 summarizes our linear regression analysis. The first two blocks of the table present the results with the inclusion of the additional control variables. Although the sign of the regression coefficient (B) obtained for BMI was positive as expected, the contribution of the variable did not emerge to be statistically significant. At the same time, the higher age was found to reduce the expected value of the Epworth index at $P<0.05$ critical values. 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. When choosing GERD 0 as the reference category (that is the indicator for this group was excluded), the coefficients for the sub-groups of GERD I-III took positive and increasing values as it is shown by the figures of the first model. These coefficients reached a critical magnitude at the GERD III group, which already proved to be significant at 5% level. 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 the third sub-group of GERD I-III. The negatively

Table 3 Linear regression and dependent variable: Epworth index

	Reference: GERD 0 & control variables			Reference: GERD III & control variables			Reference: GERD 0			Reference: GERD III		
	B	*t*-stat	Signif	B	*t*-stat	Signif	B	*t*-stat	Signif	B	*t*-stat	Signif
Constant	5.210	2.370	0.019	8.743	3.653	0.000	6.708	7.748	0.000	10.769	9.155	0.000
GERD 0				-3.534	-2.410	0.018				-4.061	-2.780	0.006
GERD I	0.503	0.433	0.666	-3.031	-2.125	0.036	0.464	0.397	0.692	-3.597	-2.541	0.012
GERD II	0.635	0.610	0.543	-2.899	-2.178	0.031	0.685	0.662	0.510	-3.376	-2.586	0.011
GERD III	3.534	2.410	0.018				4.061	2.780	0.006			
BMI	0.092	1.254	0.212	0.092	1.254	0.212						
NEM	-0.002	-0.003	0.998	-0.002	-0.003	0.998						
AGE50	-1.557	-1.999	0.048	-1.557	-1.999	0.048						
						n =122						

Table 4 Logistic regression , dependent variable: "abnormal" EPWORTH

	Reference: GERD 0 & control variables				Reference: GERD III & control variables				Reference: GERD 0				Reference: GERD III			
	B	Wald-stat	Signif	Odds ratio	B	Wald-stat	Signif	Odds ratio	B	Wald-stat	Signif	Odds ratio	B	Wald-stat	Signif	Odds ratio
Constant	-0.399	0.153	0.695		-0.399	0.153	0.695		-0.079	0.119	0.729		-0.079	0.119	0.729	
GERD		6.547	0.087			6.547	0.087			7.452	0.058			7.452	0.058	
GERD 0					-1.996	6.126	0.013	0.136					-2.091	6.887	0.008	0.124
GERD I	0.404	0.461	0.497	1.498	-1.592	4.234	0.039	0.204	0.394	0.447	0.503	1.484	-1.696	4.963	0.025	0.183
GERD II	0.704	1.748	0.186	2.023	-1.292	3.118	0.077	0.275	0.744	2.025	0.154	2.104	-1.347	3.592	0.058	0.260
GERD III	1.996	6.126	0.013	7.361					2.091	6.887	0.008	8.095				
BMI	0.023	0.406	0.523	1.023	0.023	0.406	0.523	1.023								
NEM	-0.166	0.174	0.675	0.847	-0.166	0.174	0.675	0.847								
AGE50	-0.408	1.112	0.291	0.664	-0.408	1.112	0.291	0.664								
							n=122									

signed coefficients with decreasing absolute values that were estimated relative to GERD III directly mirrored the results of the first model, but this regression exercise gave an opportunity for further statistical tests (see the second block). Thus, the coefficients obtained for GERD 0 as well as for GERD I, II were significantly (P<0.05) different from zero, and consequently indicated statistically relevant deviations from the expected Epworth value at GERD III serving as the baseline. These two estimations above were repeated without the additional control variables as well (see the third and fourth blocks of Table 3). The coefficients in this case were of course equivalent with the differences of the Epworth means grouped in Table 2. 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" as it is presented in Table 4. The sign of the coefficients (B) obtained for the additional control variables was the same as in the case of the linear regression, but we could not identify a separate significant effect in this case on the basis of the Wald-tests. At the same time, the Wald-statistic referring to the joint effect of the GERD categories (i.e. the "GERD" row of the table) already displayed a weakly significant (P<0.1) value. The estimates relative to GERD 0 gave again increasing coefficients with odds ratios greater than one (see the parameters of the first model). 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. At the same time, the increasing odds ratios with values lower than one derived from the logistic regression using GERD III as the reference category showed statistically significant differences in the case all less severe reflux disease groups (the second block of the table). (In this respect, GERD II could be regarded as a "transitory" category between GERD III and the milder disease classes as far as this difference appeared to be only weakly significant.) The regressions re-run without the control variables produced the odds ratios that could be directly calculated from the frequencies of Table 2 (see the third and fourth models of Table 4). 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.

DISCUSSION

We raised the question whether the well-known nocturnal symptoms of patients suffering from GERD results in the deterioration of daytime cognitive functions. 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 reaches 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[4,16]. The higher positioned and longer than 5 min 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[17]. This irritation would lead to the change in muscle tone as a manifestation of arousal producing a motoric restless sleep. In addition, the regurgitation of the acidic gastric fluid may cause discomfort, choking, aspiration, and disturbed sleep with multiple awakenings. The motoric restless sleep is more likely to happen even independently of the pH value of the gastric content, if the refluxate reaches the sensitive pharyngeal level. We, however only assessed patients with the classical self-reported GERD. In fact, patients with extra esophageal symptoms may develop daytime somnolence even earlier and without visible esophagitis.

Finally, it should be noted that GERD is not the dysfunction of acid production but the insufficiency of the LES. So it is important to explore daytime somnolence in the cases of severe and therapy refractory GERD[18]. These cases can be caused by sleep-related breathing disorders, which can augment the symptoms of GERD and cause daytime sleepiness as well.

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