

## Prevalence of Attention Deficit Hyperactivity Disorder in Pediatrics Patients Newly Diagnosed with Gastroesophageal Reflux Disease

Mohammad Effatpanah<sup>1</sup>, Farzaneh Motamed<sup>2</sup>, Mehri Najafi<sup>2</sup>, Fatemeh Farahmand<sup>2</sup>, Gholamhossein Fallahi<sup>2</sup>, \*Davood Motaharizad<sup>2</sup>, Mir Saeed Yekaninejad<sup>3</sup>, Mostafa Qorbani<sup>4</sup>, Jayran Zebardast<sup>5</sup>

<sup>1</sup>School of Medicine, Ziaei Hospital, International Campus, Tehran University of Medical Sciences, Tehran, Iran. <sup>2</sup>Child and Adolescent's Medical Center, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran. <sup>3</sup>Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran. <sup>4</sup>Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran. <sup>5</sup>Deputy of Research, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran.

### Abstract

**Background:** Gastroesophageal reflux disease (GERD) is associated with a number of comorbidities in pediatrics. However, its association with attention deficit hyperactivity disorder (ADHD) has not been reported. The aim of the present study was to investigate the prevalence of ADHD in pediatric patients newly diagnosed with GERD.

**Materials and Methods:** Sixty newly-diagnosed treatment naive GERD patients and sixty healthy controls aging between 5 to 12 years referring to the Children and Adolescent's medical center, Tehran, Iran were recruited in a case-control study during the year 2015. Then patients were evaluated for ADHD by a psychiatrist according to the DSM-IV criteria. The revised Conners' Parent Rating Scale (CPRS-R) was used for assessment of the symptoms of ADHD. To screen for psychiatry disorders other than ADHD, the Kiddie-Sads-Present and Lifetime Version (K-SADS-PL) questionnaire was used. Logistic regression analysis was used for modeling the association between GERD and ADHD in the study sample.

**Results:** The mean age of GERD patients was  $5.77 \pm 2.27$  and for non-GERD controls was  $6.03 \pm 2.52$  ( $P = 0.543$ ). Thirty-three out of 60 (55%) GERD patients and 37 out of 60 (61.66%) non-GERD controls were male ( $P = 0.579$ ). Prevalence of ADHD was 33.60 (55%) in GERD patients and 10.60 (16.66%) in non-GERD ( $P < 0.001$ ). Data analysis revealed that being diagnosed with GERD was associated with higher odds of ADHD diagnosis ( $P < 0.001$ ; odds ratio [OR]: 6.88, 95% confidence interval [CI]: 2.8-16.9).

**Conclusion:** According to the results, diagnosis of GERD was associated with higher odds of being diagnosed with ADHD.

**Key Words:** ADHD, Children, Gastroesophageal reflux disease, Comorbidity.

\*Please cite this article as: Effatpanah M, Motamed F, Najafi M, Farahmand F, Fallahi Gh, Motaharizad D, et al. Prevalence of Attention Deficit Hyperactivity Disorder in Pediatrics Patients Newly Diagnosed with Gastroesophageal Reflux Disease. Int J Pediatr 2017; 5(9): 5609-16. DOI:10.22038/ijp.2017.23529.2002.

### Corresponding Author:

Davood Motaharizad, MD, Child and Adolescent's Medical Center, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran.

Email: motaharizad49@gmail.com

Received date: Apr.10, 2017; Accepted date: Jun.22, 2017

## 1- INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD), marked by an ongoing pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development in the children, is a common pediatric neurobehavioral disorder which requires timely medical attention (1). The exact etiology of the disorder has not been fully understood. Twin studies have demonstrated the contribution of genetic risk factors in the pathogenesis of the disorder (2). ADHD affects around 5 to 12% of school-age children (3-5). ADHD is known to be associated with a wide range of human behavioral disorders including anti-social behavior, learning disorders, substance abuse, communication problems and other psychiatric associated disorders (3-7).

Patients are usually to present the manifestations of other medical problems such as febrile convulsion in infants as well as visual problems including vision problems, respiratory system diseases such as asthma, allergic disease, thyroid disease, obesity, heart disease and urology problems (5-10). To these should be added the diseases of the gastrointestinal (GI) diseases such as diarrhea, constipation, abdominal pain, and other chronic bowel complications (4, 8, 11-14).

Gastroesophageal reflux (GER) is a physiologic process occurs in over 70% of infants several times a day, but it usually disappears by the age of 12-14 months. Gastroesophageal reflux disease (GERD) is a pathologic form of GER which lasts more than this age and causes troublesome symptoms and may be associated with further complications. GERD is a common disorder of the digestive system defined by the backflow of the contents of the stomach into esophagus leading to troublesome symptoms and/or complications. GERD prevalence in adults has been estimated to be 3.8% in Chinese population (15), 3.3% in Japanese

population (16), around 20 % in Indian populations (17) and over 20% in the Western population (18). The estimated prevalence of the disease in North American infants is 12.3% and in older children is 1% (19). The manifestations may differ depending on the severity of the reflux. Clinical Features in GERD includes regurgitation, poor weight gain, anemia, dysphagia, irritability, pain, chest pain, heartburn, apnea, cyanosis, pneumonia, cough, stridor and neck tilting in infants (Sandifer's syndrome) (20-23). Risk factors GERD include but are not limited to congenital esophageal abnormalities and neurologic impairment (24). It is known to be associated with the pathologies of neurological system (18).

Since the previous studies have demonstrated the high prevalence of psychiatry disorders in patients with GERD (25-28) and association understood between ADHD and disease of the digestive tract (29), we sought to investigate the prevalence of ADHD in patients with GERD. Since when patients present with a diseases it is very important to be examined for the presence of other comorbidities, it is important to investigate the potential association between the two diseases. Therefore, we conducted the current study to examine the prevalence of ADHD in patients newly diagnosed with GERD.

## 2- MATERIALS AND METHODS

### 2-1. Study design and subjects

The study design was case-control. Protocol of the study was approved by the institutional review board of the Tehran University of Medical Sciences. All ethical codes of the Declaration of Helsinki for Medical Studies including human subjects were appropriately followed. Sixty patients newly diagnosed with GERD and sixty non-GERD healthy controls aging between five to 12 years old were studied. Patients referring to Gastroenterology Clinic in

Children and Adolescent's Medical Center, Tehran University of Medical Sciences, Tehran, Iran in the year 2015 entered the study after informed consent of the guardians and when required the patients themselves. Demographic data of the study participants were recorded in questionnaires. GERD diagnosis was based on the history and physical examination and other standard methods by gastroenterology department according to the National Institute for Health and Care Excellence (NICE) guideline (30). Children with following conditions were excluded from study: IQ scoring below 70, psychiatry disorders other than ADHD, patients with chronic diseases requiring long term treatment including epilepsy, asthma, diabetes, immune deficiency, malignancies, very low birth weight (VLBW) children, congenital and chromosomal abnormalities and intellectual disability.

## 2-2. ADHD diagnosis

Subjects were referred to the psychiatry clinic for examination for ADHD. The revised Conners' Parent Rating Scale (CPRS-R) was used for assessment of the symptoms of ADHD (31). The Persian version of the questionnaire has been demonstrated to be reliable for the diagnosis of anxiety and other psychiatric disorders in Iranian children (32). It is a semi-structured diagnostic interview with parents. The questionnaire contains forty eight questions with four-scale answers ranging from "not at all", "just a little", "pretty much" and "very much"; these answers were scored 0, 1, 2 and 3, respectively. The questionnaire was answered with parents. The higher the score, more probable the patient is to have ADHD. Patients with sum of scores higher than 60, were considered as ADHD patient. To confirm the diagnosis and screen for other psychiatry disorders, the Kiddie-Sads-Present and Lifetime Version (K-SADS-PL) questionnaire was used

(33). This questionnaire is semi-structured and was used by a psychiatry specialist.

## 2-3. Statistical analysis

Numerical data were presented as mean± standard deviation (SD) and frequency and frequency percent for qualitative data. Kolmogrov-Smirnov test and graphical presentation of the data was used to test whether the distribution of the numerical data complies with the normal distribution of the data. Between groups comparisons were performed using unpaired t-test for normally distributed numerical data and Chi-square test for qualitative data. Logistic regression analysis was used to model the risk of ADHD from GERD, age, gender and weight of the patients. Data analysis was performed by SPSS v.16.0 (IBM, USA). P-value below 0.05 was set as statistical significance level.

## 3- RESULTS

### 3-1. Descriptive and comparisons across subsamples

Patients and healthy controls were age and sex-matched and no significant differences between groups were observed in these parameters. Prevalence of ADHD between two groups was significantly different. Descriptive data are summarized in (**Table.1**). Mean age of the patients was  $5.77\pm 2.27$  and  $6.03\pm 2.52$  in GERD patients and controls ( $p=0.543$ ). Also, mean height and weight were  $112.13\pm 34.77$  and  $18.9\pm 11.3$  in patients, and  $108.95\pm 41.39$  and  $18.1\pm 9.67$  in healthy controls ( $P>0.05$  for both variables), respectively. There were no statistically significant differences in the prevalence of ADHD and GERD between male and female cases ( $P>0.05$ , **Figure.1**).

### 3-2. Logistic regression

Results of the logistic regression analysis for predicting the risk of GERD from ADHD, gender, age, height and weight of the patients are presented in (**Table.2**).

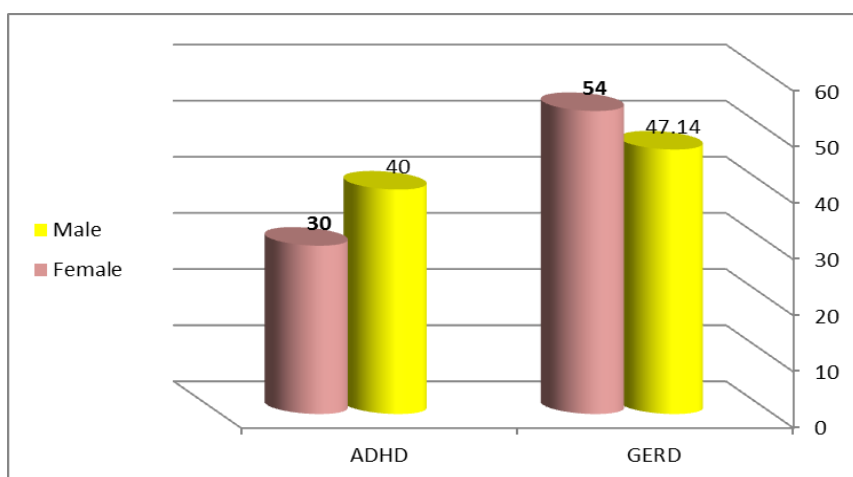
Thirty three out of 60 (55%) of GERD patients and 10 out of 60 (16.66%) of healthy controls were diagnosed with ADHD ( $P < 0.001$ ). Analysis revealed that ADHD was significantly associated with the risk of presence of GERD in the study subjects and the odds of having ADHD for a patient diagnosed with GERD was 6.88 (95% confidence interval [CI]: 2.80-16.91).

This effect was independent of the age and gender of the subjects. The odds ratio (OR) for a man to be diagnosed with ADHD was 1.66 (95% CI: 0.72-3.82,  $P = 0.236$ ) which shows no significant association between two factors. The same was observed in case of the age and ADHD diagnosis (OR: 1.03 [95% CI: 0.86-1.22,  $P = 0.764$ ]).

**Table-1:** Demographic information of the participants

Variables	Groups (mean $\pm$ SD or frequency/frequency percent)		P-value
	GERD patients	Healthy controls	
Gender (male percent)	33/60 (55%)	37/60 (61.66%)	0.579
ADHD (frequency)	33/60 (55%)	10/60 (16.66%)	<0.001
Age (years)	5.77 $\pm$ 2.27	6.03 $\pm$ 2.52	0.543
Weight (kg)	18.77 $\pm$ 2.09	19.33 $\pm$ 2.19	0.25
Height (cm)	96.0 $\pm$ 13.51	94 $\pm$ 12.09	0.558

Comparisons were made using independent samples t-test for qualitative data and chi-square test for qualitative data. GERD: Gastroesophageal reflux disease, ADHD: attention deficit hyperactivity disorder.



**Fig.1:** Prevalence of attention/deficit hyperactivity disorder (ADHD) and gastroesophageal reflux disease (GERD) in the male and female patients; the chart depicts the frequency percent of patients diagnosed with each of two diseases as two main outcome measures of the study in male and female group of patients. Values are presented as frequency percent by each gender. Statistical analysis showed no significant differences between male and female groups in case of their odds of being diagnosed with either ADHD or GERD.

**Table-2:** The Relationship between ADHD with GERD

Variables	OR (95% CI)	P-value
Gender (referent: male)	1.698 (0.719-4.011)	0.227
ADHD (referent: no)	7.130 (2.823-18.006)	<0.001
Age (years)	0.970 (0.813-1.157)	0.732
Height (cm)	0.996 (0.964-1.029)	0.802
Weight (kg)	1.174 (0.971-1.418)	0.097

OR: Odds ratio; SD: Standard deviation; The results of the logistic regression analysis for evaluation of the effects of attention/deficit hyperactivity disorder (ADHD) on gastroesophageal reflux disease (GERD) adjusted for age and gender.

#### 4- DISCUSSION

In the current study we investigated the prevalence of ADHD in pediatric patients newly diagnosed with GERD. Analysis revealed the high odds for association between these conditions. The present study is the first description of association between ADHD and GERD. The association between these two disorders could be described by different hypotheses. Since we have chosen our study samples from newly diagnosed patients who have not received any treatment, either pharmacological or behavioral, the association could not be the effect of interventions intended for the treatment of either disease. The association could hint a common pathogenic mechanism which is implicated in both of the diseases. GERD has been demonstrated to be associated with behavioral problems. Böhmer et al. demonstrated that GERD is highly prevalent in institutionalized intellectually disabled individuals (34).

Other studies have demonstrated the adverse effects of GERD on patients quality of life and behavior which may be direct consequence of the disease (35). Patients often have problem sleeping and mood disorders (28, 36). Kamolz and Velanovich have extensively discussed the psychological and physiological aspects of esophageal and other gastrointestinal symptoms. They suggested the biopsychosocial model of the disease which implies a close relationship between psychological conditions and disorders of

the digestive system including GERD (27). According to Fujiwara et al., GERD is associated with sleep disorders (37, 38). The same observation has been made with several other independent studies (26, 39-41). Martín-Merino et al., demonstrated the high prevalence of GERD in patients receiving anti-depressants (42). This could be attributed to the effects of anti-depressants on the onset of GERD. You et al., have demonstrated the high prevalence of psychiatric disorders in GERD patients. In their study the risks of depressive disorder, anxiety disorder and sleep were higher in the GERD cohort than in the comparison cohort (25). Other studies have implied a wide range of comorbidities associated with GERD.

These comorbidities include, but are not limited to the arterial hypertension, hypercholesterolemia, obesity, type II diabetes mellitus, depression, arthritis, depression, osteoporosis, asthma and constipation (43). Another study by Mized et al., have demonstrated the presence of a wide spectrum of psychological comorbidities including bipolar disorder, major depression, paranoid schizophrenia, schizophrenia, alcohol dependence, polysubstance abuse and borderline personality in patients with GERD (44).

However, there has been no report on the prevalence of ADHD in patients with GERD. Present study is the first study to describe the association between the ADHD, as a psychiatric condition, with the

GERD, as a disorder of the digestive system. It is not possible to draw a conclusion regarding the type of association between these two conditions. However, since the odds of association is dramatically high we suggest that patients with GERD to be tested for ADHD. Furthermore, we suggest further studies to validate the findings of the current study and define the interaction, if any, between these two conditions, biological relevance of the conditions and mechanisms associated with the presumed interactions.

## 5- CONCLUSION

Since GERD is associated with psychiatric conditions, clinicians should pay attention to the psychiatric comorbidities of the GERD including ADHD. Further studies are warranted for deeper understanding of the association between GERD and ADHD for appropriate and timely management of the conditions.

**6- CONFLICT OF INTEREST:** None.

## 7- ACKNOWLEDGEMENT

We acknowledge the staff of Gastroenterology Clinic in Children and Adolescent's Medical Center, Tehran University of Medical Sciences, Tehran, Iran.

## 8- REFERENCES

1. Sanchez ED, Gremse DA. Gastroesophageal Reflux in Infants and Children. 2003. Available at: [http://www.turner-white.com/pdf/brm\\_PM\\_V1P1\\_03.pdf](http://www.turner-white.com/pdf/brm_PM_V1P1_03.pdf).
2. Mohammed I, Cherkas LF, Riley SA, Spector TD, Trudgill NJ. Genetic influences in gastro-oesophageal reflux disease: a twin study. *Gut*. 2003;52(8):1085-89.
3. Yousefichaijan P, Salehi B, Shekholeslami H, Hashemi M, Sharafkhah M, Amiri M, et al. Is Attention Deficit Hyperactivity Disorder more Prevalent in

Children with functional constipation? *Sch.J.App.Med.Sci*. 2015;3(1C): 209-13.

4. Chou I-C, Chang Y-T, Chin Z-N, Muo C-H, Sung F-C, Kuo H-T, et al. Correlation between epilepsy and attention deficit hyperactivity disorder: a population-based cohort study. *PLoS One*. 2013;8(3):e57926.

5. Rowland AS, Lesesne CA, Abramowitz AJ. The epidemiology of attention- deficit/hyperactivity disorder (ADHD): a public health view. *Ment Retard Dev Disabil Res Rev*. 2002;8(3):162-70.

6. Richer LP, Shevell MI, Rosenblatt BR. Epileptiform abnormalities in children with attention-deficit-hyperactivity disorder. *Pediatr Neurol*. 2002;26(2):125-9.

7. Pineda DA, Lopera F, Palacio JD, Ramirez D, Henao GC. Prevalence estimations of attention-deficit/hyperactivity disorder: differential diagnoses and comorbidities in a Colombian sample. *Int J Neurosci*. 2003;113(1):49-71.

8. Cardo E, Amengual-Gual M. [Is attention deficit hyperactivity disorder associated with other prevalent pathologies of early childhood?]. *Rev Neurol*. 2015;60:S109-13.

9. Cutuli J, Herbers JE, Rinaldi M, Masten AS, Oberg CN. Asthma and behavior in homeless 4-to 7-year-olds. *Pediatrics*. 2010;125(1):145-51.

10. Fasmer OB, Halmøy A, Eagan TM, Oedegaard KJ, Haavik J. Adult attention deficit hyperactivity disorder is associated with asthma. *BMC Psychiatry* 2011;11(1):128.

11. Yuksel H, Sogut A, Yilmaz O. Attention deficit and hyperactivity symptoms in children with asthma. *J Asthma*. 2008;45(7):545-7.

12. Grizenko N, Shayan YR, Polotskaia A, Ter-Stepanian M, Joobar R. Relation of maternal stress during pregnancy to symptom severity and response to treatment in children with ADHD. *J Psychiatry Neurosci*. 2008;33(1):10.

13. Amiri S, Fakhari A, Golmirzaei J, Mohammadpoorasl A, Abdi S. Tourette's syndrome, chronic tics, and comorbid attention

deficit/hyperactivity disorder in elementary students. *Arch Iran Med.* 2012;15(2):76-8.

14. Malek A, Amiri S, Abdi S. Previous medical history of diseases in children with attention deficit hyperactivity disorder and their parents. *Journal of Analytical Research in Clinical Medicine* 2014;2(1): 42-6.
15. Tan VP, Wong BC, Wong WM, Leung WK, Tong D, Yuen MF, et al. Gastroesophageal Reflux Disease: Cross-Sectional Study Demonstrating Rising Prevalence in a Chinese Population. *Journal of clinical gastroenterology.* 2016;50(1):e1-7.
16. Miwa H, Takeshima T, Iwasaki K, Hiroi S. Medical cost, incidence rate, and treatment status of gastroesophageal reflux disease in Japan: analysis of claims data. *Journal of medical economics* 2016;19(11):1049-55.
17. Wang HY, Leena KB, Plymoth A, Hergens MP, Yin L, Shenoy KT, et al. Prevalence of gastro-esophageal reflux disease and its risk factors in a community-based population in southern India. *BMC gastroenterology* 2016;16:36.
18. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut.* 2005;54(5):710-7.
19. van der Pol RJ, Smits MJ, Venmans L, Boluyt N, Benninga MA, Tabbers MM. Diagnostic accuracy of tests in pediatric gastroesophageal reflux disease. *The Journal of pediatrics* 2013;162(5):983-7 e1-4.
20. Hassall E, Kerr W, El-Serag HB. Characteristics of children receiving proton pump inhibitors continuously for up to 11 years duration. *J Pediatr.* 2007;150(3):262-7. e1.
21. Gunnarsdottir A, Stenstrom P, Arnbjornsson E. 48-hour wireless oesophageal pH-monitoring in children: are two days better than one? *Eur J Pediatr Surg.* 2007;17(6):378-81.
22. Chen C-L, Orr WC. Analysis of 24-hour esophageal pH monitoring: the effect of state of consciousness. *Curr Gastroenterol Rep.* 2008;10(3):258-62.
23. Orenstein SR. Infantile reflux: different from adult reflux. *Am J Med.* 1997;103(5):114S-9S.
24. Roman S, Kahrilas PJ. The diagnosis and management of hiatus hernia. *BMJ.* 2014;349:g6154.
25. You ZH, Perng CL, Hu LY, Lu T, Chen PM, Yang AC, et al. Risk of psychiatric disorders following gastroesophageal reflux disease: a nationwide population-based cohort study. *Eur J Intern Med.* 2015;26(7):534-9.
26. Ju G, Yoon IY, Lee SD, Kim N. Relationships between sleep disturbances and gastroesophageal reflux disease in Asian sleep clinic referrals. *J Psychosom Res.* 2013;75(6):551-5.
27. Kamolz T, Velanovich V. Psychological and emotional aspects of gastroesophageal reflux disease. *Dis Esophagus.* 2002;15(3):199-203.
28. Sanna L, Stuart AL, Berk M, Pasco JA, Girardi P, Williams LJ. Gastro oesophageal reflux disease (GORD)-related symptoms and its association with mood and anxiety disorders and psychological symptomatology: a population-based study in women. *BMC Psychiatry* 2013;13:194.
29. Aksglæde K, Pedersen J, Lange A, Funch-Jensen P, Thommesen P. Gastro- Esophageal Reflux Demonstrated by Radiography in Infants Less Than 1 Year of Age. *Acta Radiol.* 2003;44(2):136-8.
30. Davies I, Burman-Roy S, Murphy MS, Guideline Development G. Gastro-oesophageal reflux disease in children: NICE guidance. *BMJ.* 2015;350:g7703.
31. Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol.* 1998;26(4):257-68.
32. Ghanizadeh A. ADHD, bruxism and psychiatric disorders: does bruxism increase the chance of a comorbid psychiatric disorder in children with ADHD and their parents? *Sleep Breath.* 2008;12(4):375-80.
33. Mohammadi MR, Ahmadi N, Salmanian M, Asadian-Koohestani F, Ghanizadeh A, Alavi A, et al. Psychiatric

Disorders in Iranian Children and Adolescents. Iranian journal of psychiatry 2016;11(2):87-98.

34. Bohmer CJ, Niezen-de Boer MC, Klinkenberg-Knol EC, Deville WL, Nadorp JH, Meuwissen SG. The prevalence of gastroesophageal reflux disease in institutionalized intellectually disabled individuals. *Am J Gastroenterol* 1999;94(3):804-10.

35. Wiklund I. Review of the quality of life and burden of illness in gastroesophageal reflux disease. *Dig Dis*. 2004;22(2):108-14.

36. Jansson C, Nordenstedt H, Wallander MA, Johansson S, Johnsen R, Hveem K, et al. A population-based study showing an association between gastroesophageal reflux disease and sleep problems. *Clin Gastroenterol Hepatol*. 2009;7(9):960-5.

37. Fujiwara Y, Habu Y, Ashida K, Kusano M, Higuchi K, Arakawa T. Sleep disturbances and refractory gastroesophageal reflux disease symptoms in patients receiving once-daily proton pump inhibitors and efficacy of twice-daily rabeprazole treatment. *Digestion* 2013;88(3):145-52.

38. Fujiwara Y, Arakawa T, Fass R. Gastroesophageal reflux disease and sleep disturbances. *J Gastroenterol* 2012;47(7):760-9.

39. Iwakura N, Fujiwara Y, Shiba M, Ochi M, Fukuda T, Tanigawa T, et al.

Characteristics of Sleep Disturbances in Patients with Gastroesophageal Reflux Disease. *Intern Med*. 2016;55(12):1511-7.

40. Okuyama M, Takaishi O, Nakahara K, Iwakura N, Hasegawa T, Oyama M, et al. Associations among gastroesophageal reflux disease, psychological stress, and sleep disturbances in Japanese adults. *Scand J Gastroenterol*. 2017;52:44-9. DOI: 10.1080/00365521.2016.1224383

41. Karoui S, Chtara O, Bibani N, Kallel L, Zouiten L, Matri S, et al. Sleep disorders in patients with gastroesophageal reflux disease: an open clinical and pH metric prospective study. *Tunis Med*. 2010;88(3):172-7.

42. Martin-Merino E, Ruigomez A, Garcia Rodriguez LA, Wallander MA, Johansson S. Depression and treatment with antidepressants are associated with the development of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2010;31(10):1132-40.

43. Moraes-Filho JP, Navarro-Rodriguez T, Eisig JN, Barbuti RC, Chinzon D, Quigley EM. Comorbidities are frequent in patients with gastroesophageal reflux disease in a tertiary health care hospital. *Clinics*. 2009;64(8):785-90.

44. Mized I, Fass SS, Fass R. Review article: gastro-oesophageal reflux disease and psychological comorbidity. *Aliment Pharmacol Ther*. 2009;29(4):351-8.