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Original Article / Оригинални рад

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Is there a difference between patients with functional dyspepsia and irritable bowel syndrome in headache manifestation?

Постоји ли разлика у манифестацији главобоље између пацијената са функционалном диспепсијом и синдромом иритабилног црева?

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Постоји ли разлика у манифестацији главобоље између пацијената са функционалном диспепсијом и синдромом иритабилног црева?

SUMMARY

Introduction/Objective The objective was to explore whether there is a difference in headache manifestation and level of its intensity in patients with functional dyspepsia and irritable bowel syndrome.

Methods We assessed a cohort of N=420 participants out of which N=300 satisfied presence of irritable bowel syndrome (148) or functional dyspepsia (152) as a recruiting criterion. Diagnoses of irritable bowel syndrome and functional dyspepsia were made according to Rome IV criteria. Intensity of headaches was estimated in irritable bowel syndrome and functional dyspepsia participants using visual-analog scale. All patients underwent subsequent testing by Hamilton's depression inventory and anxiety scale.

Results Our results showed that males with headaches are more susceptible to functional dyspepsia, statistical significance in the group of patients with irritable bowel syndrome with high scores visual analog scales, in relation of Hamilton's anxiety scores in the group of patients with irritable bowel syndrome. Gender and visual analogue scale scores were determinants to show whether the patient falls within the group of functional dyspepsia or irritable bowel syndrome. Scores of visual analogue scale where the patient felt the best was statistically borderline (p = 0.061) and its higher values pinpointed which of those patients fall into irritable bowel syndrome group.

Conclusion Gender and level of headache intensity as a extraintestinal manifestation showed to be the main variables to make a difference between patients with functional dyspepsia and irritable bowel syndrome where irritable bowel syndrome had higher scores and greater dominance in differential diagnosis if the headache was determining variable.

Keywords: headaches; functional dyspepsia; irritable bowel syndrome

САЖЕТАК

Увод/Циљ Циљ овог истраживања је да утврди да ли постоји разлика у манифестацији главобоље и степеном њеног интензитета у пацијената са функционалном диспепсијом и синдромом иритабилног црева.

Методе Група испитаника сачињавала је 420 пацијената од којих је 300 задовољило укључујуће критеријуме у виду присуства синдрома иритабилног црева (148) или функционалне диспепсије (152). Дијагнозе синдрома иритабилног црева и функционалне диспепсије постављене су у складу са Рома ИВ критеријумима. Интензитет главобоља процењен је у групама пацијената са синдромом иритабилног црева и функционалном диспепсијом помоћу визуелно-аналогне скале. Сви пацијенти подвргнути су тестирањем помоћу Хамилтонове скале депресије и скале анксиозности.

Резултати Наши резултати показују да су мушкарци са главобољом подложнији функционалној диспепсији као и да постоји статистички значајна разлика у групи пацијената са иритабилним синдромом црева који су имали веће резултате на визуелно – аналогној скали И статистички значајна разлика у погледу резултата скале анксиозности у групи пацијената са синдромом ирититабилног црева. Пол и резултати на визуелно –аналогној скали биле детерминанте одређивања да ли пацијент припада групи функционалне диспепсије или синдрома иритабилног црева. Резултати на визуелно-аналогној скали где су пацијенти навели да се најбоље осећају били су гранично статистики значајни (p = 0.061) и њихова већа вредност истакла је оне пацијенте који припадају групи синдрома иритабилног црева.

Закључак Пол и ниво интензитета главобоље као екстраинтестиналне манифестације представљају главне варијабле за утврђивање разлике између пацијената са функционалном диспепсијом и синдромом иритабилног црева, где синдром иритабилног црева има веће резултате и доминацију у диференцијалној дијагнози уколико је главобоља детерминишућа варијабла.

Кључне речи: главобоље; функционална диспепсија; синдром иритабилног црева

INTRODUCTION

Migraine is a primary headache typically characterized by unilateral pulsating head pain that is aggravated by routine physical activity and may be accompanied by a variety of autonomic, cognitive, and emotional disturbances [1]. Headaches are reported to be evaluated as one of the top rated self-reported physical disorders [2]. Estimated 1-year prevalence of migraine is approximately 14% in the general population and the association between a headache and gastrointestinal complaints increased with increasing headache frequencies. Chronic migraine like headache was reported in about 30% patients with functional dyspepsia, but the pathophysiology is still not fully understood [3, 4]. Functional gastrointestinal and motility disorders are group of disorders of gut-brain interaction which are categorized by Rome diagnostic criteria as symptom based diagnostic criteria for each category [5]. Due to the fact that the prevalence of functional digestive disorders and irritable bowel syndrome are still underestimated with the currently applied diagnostic tools, some other improved criteria or point of view is needed as the treatment is not still very efficient and satisfactory. Irritable bowel syndrome (IBS) presents a neurogastroenterological functional disorder that shares some environmental risk factors with a migraine (predominately affecting the female sex and younger individuals). It is a group of bowel disorders with specific abdominal discomfort or pain correlated with bowel habit irregularities. Functional dyspepsia (FD) refers to pain or specific discomfort in the topographic region of upper abdomen. Irritable bowel syndrome and functional dyspepsia share many somatic and psychiatric comorbidities [6]. Except for the headaches as one of the most prominent extraintestinal neurological manifestation, globus hystericus presents one of esophageal disorders manifesting as a sensation of a lump or tightness in the throat, which also can be attributed to psychogenic cause i.e., somatoform or anxiety disorder [7].

The objective was to explore whether there is a difference in headache manifestation and to evaluate the level of its intensity in patients with functional dyspepsia and irritable bowel syndrome.

METHODS

We assessed a cohort of N=420 participants out of which N=300 (174 females and 126 males) satisfied presence of irritable bowel syndrome (148) or functional dyspepsia (152) as a recruiting criterion. All participants were informed about the study protocol and they provided written consent. The study was approved by the Ethical Committee of Clinical and Hospital Center "Dr Dragisa Misovic - Dedinje" (18-6685/2019). Participants were 18 to 80 years old and referred to the gastroenterology unit of the Clinical and Hospital Center " Dr Dragisa Misovic - Dedinje" from January to December 2019. Diagnoses of IBS and FD were made according to Rome IV criteria [5]. Participants satisfied the following inclusion criteria: 1) Older than 18 years; 2) No evidence of organic disease on the upper and lower endoscopy examination; 3) Normal findings on abdominal ultrasonography; 4) No history of abdominal surgery; 5) Absence of any cardiovascular or metabolic disease to avoid vasculoprive or headaches related to the impaired metabolism or endocrine function; and 6) No evidence about prior neuropsychiatric treatment.

Participants underwent a clinical interview and physical and neurological examinations by experienced neurologists in order to exclude headaches associated with neurological disorders and to assess for presence of migraine-like migraine. A migraine has been diagnosed according to International Classification of Headache Disorders 3rd edition [8].

The intensity of headaches has been estimated in IBS and FD participants using visual analog scale (VAS) where 0 is absence of pain and 10 is the worst possible pain. VAS scale was used to assess pain in three states: pain when the patient was at his/hers best (VAS best), baseline pain (VAS typical), and pain when patient was at his/hers worst (VAS worse). Please note, we reanalyzed data from our two groups (IBS, N =148 and FD, N=152) to determine the mean of VAS pain intensity rating and changes scores on 10 cm rating scale, 0 – 0. 4 cm considered no pain; 0.5 – 4.4 cm mild 4.5 – 7.4 cm moderate pain, and 7.5 – 10 cm severe pain.

Participants underwent psychiatric examination including psychiatric interview/evaluation by the specialist of psychiatry in order to assess for presence of depressive or anxiety disorder and to exclude other psychiatric co-morbidities. Patients underwent subsequent testing by Hamilton's anxiety (HA) and depression (HD) 21-item inventory, Serbian version [9]. Typically, Hamilton depression inventory contain items related to gastrointestinal symptoms and weight loss. Please note that these were omitted because the mentioned symptomatology is part of the illness. The diagnosis of globus hystericus (GH) has

been made according to 10th revision of the International Classification of Diseases (ICD–10) criteria for the diagnosis code F 45.8 [7]. The presence of GH was assessed by routine questionnaire used during the first visit to the gastroenterologist.

Statistical analysis

We used Pearson's chi test with likelihood ratio correction to compare groups among categorical data when necessary. For those variables expressed with the scores, testing was performed to verify if the normal distribution exists and, in that case, we used the Kolmogorov Smirnov test. Non-parametric test methods were used for further analysis. The Mann Whitney test was used to compare the parameters on the scale to determine the difference. A binomial logistic regression analysis, the stepwise backward method, was used to define the determining variables that may be influencing the prediction of group affiliation. We used the software program SPSS 27, with a significance threshold of $p = 0.05$.

Ethics approval and consent to participate

The protocol involving human data was in accordance with national and institutional guidelines and the Declaration of Helsinki. All participants were informed about the study protocol and they provided written consent. The study was approved by the Ethical Committee of Dr. Dragiša Mišović – Dedinje Clinical and Hospital Center (18-6685/2019).

RESULTS

Demographic data imply that examined groups were of similar size ($p = 0.808$), gender-balanced with slightly more women within examined groups ($p = 0.122$). The manifestation and occurrence of headaches is less pronounced according to our results but not statistically significant ($p = 0.073$). Manifestation of globus hystericus and scores of HA were almost completely uniform within the observed categories ($p = 0.755$ and $p = 0.949$). The HD scores were mostly uniform and did not show a statistically significant difference ($p = 0.271$). The scores of HD, HA, VAS as well as the ages of examined patients did not have a normal distribution, therefore we used non-parametric tests and based our results on Mann Whitney

test. In all cases, the groups were uniform ($p> 0.05$) and at the very beginning did not differ according to the observed parameters (Tables 1 and 2).

Demographic data showed no statistical difference between FD and IBS groups ($p>0.05$). Table 1.

VAS score and Hamilton scales showed no difference between examined groups when Mann Whitney test was done, but when we made a separation into groups who had headaches and had not headaches, the statistical significance was shown in male patients with FD, which is shown in Table 2.

Since the headache was found as one of the dominant determinant variables in logistic regression analysis, the influence of the determining variable between examined groups and observed variables was measured. (Table 3).

Sex (gender) had an impact on FD and IBS when related to headache, as seen in Table 4. Males with headaches are more susceptible to FD, HR=1.829 (1.043-3.206).

Globus hystericus, HD, HA show no statistical difference between groups if headache is observed as determining variable ($p>0.05$).

In scores VAS (worse and best) there was a statistical significance between FD and IBS where IBS had higher scores if the headache is determining variable. Opposite to this, in situation without headache only HA scale showed some upper limits in IBS group of patients as statistically significant ($p< 0.05$). (Table 5.)

In the group of those who had headache using logistic regression showed determining variable within each examined group and sex (gender), VAS best, VAS typical and VAS worse determined whether patient falls within the group of FD or IBS. VAS best was statistically borderline ($p=0.061$). Higher VAS best score shows HR=1.410 (0.984-2.020) which pinpoints that those patients fall into IBS group. VAS typical shows less hazard to be IBS if scores are higher HR=0.577 (0.377-0.884). VAS worse shows more important role to determine IBS group with HR=2.191 (1.273-3.771).

In situation without headache the only important variable is HA where HR score shows to fall within the scope of IBS with higher values HR=1.092 (1.022-1.166). (Table 6.)

DISCUSSION

There is a great overlap between functional dyspepsia and irritable bowel syndrome clinical manifestation. Headaches, especially migraines, present one of the most important and disabling manifestations in above mentioned gastrointestinal disorders, proving very important and powerful role of brain-gut axis. [4, 10].

In our study we used presence of headaches and relation to their specific intensity (VAS scale scores) based on which we made a separation between patients with functional dyspepsia and irritable bowel syndrome.

Headaches like migraine present a very disabling condition, often recurrent and severe with concomitant gastrointestinal features and affects more women than men [11]. It was also shown that functional dyspepsia affects women more than men in daily life [12].

Our results showed that gender had an impact on FD and IBS when related to headache showing that males with headaches are more susceptible to FD. When we made a separation into groups who had headaches and had not headaches, the statistical significance was shown in group of male patients with FD. In previous studies conducted related to gender differences in migraines it was shown that man tend to have longer remission periods than women and that headache attack frequency and their intensity are similar to both genders with severe migraines persisting longer in women [13].

The visual analog score (VAS) evaluates the severity of subjective symptoms in patients, especially in measuring pain. Our results showed that there is statistical significance in the group of patients with IBS who had high scores VAS scales which correlates with previous studies.

Migraine headaches have a higher prevalence in patients with IBS compared to that of the general population. Li et al showed that patients with reported chronic headaches are more likely to have IBS [14].

Our results also showed statistical significance in relation of HA scores in the group of patients with IBS. Anxiety presents a psychiatric disorder which attacks individuals with IBS and therefore might worsen their condition. The reason lies in the fact that colon as an anatomical substrate is under control of nervous system responding to stress. Affected HPA axis activates stress biochemical cascade which triggers immune system as well which plays a

significant role. Although anxiety itself mostly doesn't cause gastrointestinal disorder, these patients are more emotional to everyday life stressors.

When we analyzed all significant variables in the group of patients with headaches, our results showed that gender, VAS best, VAS typical and VAS worse were determinants whether patient falls within the group of FD or IBS. VAS best was statistically borderline and higher VAS best score pinpointed which of those patients fall into IBS group. Generalized inflammatory response rather than isolated bowel inflammation may play the key role in the pathogenesis of the extra-intestinal manifestations of IBD.

Activation of hypothalamic-pituitary axis (HPA) was associated with stress and increase of IL-6 in peripheral blood. There is also relationship between inflammation and mental disorders in patients with anxiety and depression that had immune response which correlated to increase serum C-reactive protein and other inflammatory mediators [15, 16, 17].

Patients with overlap of IBD and FD symptoms had more severe psychological problems and problems with anxiety and depression as an independent factor [18].

It has been hypothesized that the underlying pathophysiology for both, IBS and migraine, is a genetically established hypersensitive or hyperexcitable brain [19]. Environmental, psychological, and immunological factors may increase sensitization in the enteric nervous system and brain gut axis in IBS. Increased amygdala activity, demonstrated in IBS [20], could also be linked with the conversion dysphagia, also known as globus hystericus and subsequent influence to the emotional zones. Abnormalities in emotion regulation and connectivity have been identified, in non-symptom studies about conversion disorders, potentially pointing to a diathesis or vulnerability: two studies found an abnormal emotion-motor connectivity, and a failure of normal habituation [21].

Many researchers debated about precise pathophysiological mechanisms of migraines and one of them is vascular due to the vasodilatation of the middle meningeal artery and middle cerebral artery on the side of the brain where the pain occurs, or bilaterally if the pain attacks from the both sides. It is mostly considered that the inflammation is the core mechanism and that the inflammatory mediators play the main role. Among the others the most important and the oldest histamine as well as TNF α [17].

The link between depressive and anxiety symptomatology with functional gastrointestinal disorders clinical symptoms may refer to low concentration of serotonin (5-HT) which correlates to greater nociception of trigeminal neurons which also gives a clinical correlation to different migraine intensity in pain [22]. Serotonin 5-HT1F receptor agonists are on the list of prophylactic drugs for migraine, implying that the smaller concentration of serotonin decreases stimulation of the mentioned receptors which are hypothesized to have an important role in migraine genesis [23, 24]. Moreover, probiotics are believed to be of potential benefit in the treatment of migraine, but also IBS and FD [25].

The results from a double-blind randomized controlled experimental investigation showed based evidence of correlation between irritable bowel syndrome and migraine showing expressed immunoglobulin G antibodies reduced frequency and level of migraine attacks after specific food deprivation and reduction which pinpoints the growing significance of gut-brain axis [26].

There are also evidences showing correlation between pain related functional gastrointestinal disorders and migraine in pediatric population as well as many evidences based on association of anxiety, depression and functional dyspepsia [27].

Finally, migraine in functional disorders of the gastrointestinal tract is interpreted as disrupted balance of microbiota in the gut and its influence to pain sensations and impaired brain – gut axis [15]. The concept of microbiota gut-brain axis refers to significant role of modulated enteric and central nervous system function disrupting mood and affection by modifying serotonin which plays a key role in both gastrointestinal tract and in the brain [28, 29].

Gut microbiota in correlation with gut-brain axis present define itself as the main new-to be defined axioma in functional sense of base evidence functional substrate on precise explanation of neuropsychiatric and functional gastrointestinal disorders interaction. Management options of headaches which are typically diagnosed very late impact quality of life of a patient and therefore development of treatment regime with less potentional side-effects correlated with patients with functional gastrointestinal disorders is of huge importance. Defining morphological anatomical substrate is the main step in defining an illness or disorder but in this case, we must evaluate that the systems and their interaction understanding presents the main step in definition of functional GI disorders and migraine attacks [30].

Strengths

The study largely contributes to development and improvement of differential diagnosis and treatment of patients diagnosed with neuropsychiatric intestinal problems.

Limitations

An important limitation is that this is a referred sample. Physicians referred patients to participate in the study. This may be justified as these are hard-to-reach groups because of social cultural stigma. As these patients were 'referred', we acknowledge that there is a significant risk of selection bias (choosing a large number of people with similar characteristics or views to the initial individual identified). Data about pain intensity in migraine are depending on sincerity of the patients. Globus hystericus is a symptom, thus the subjective feeling and might be interpreted differently by patients and physicians. Nonetheless, the criteria from ICD–10 are attenuating, but not eliminating, the subjectivity. Psychiatrists were not blinded to the patients' diagnosis, because psychiatric evaluation is the part of routine treatment of IBS and FD patients.

CONCLUSION

In conclusion, according to our results, headaches and their intensity are more related to males with functional dyspepsia but higher VAS scores showed great significance in making difference between patients with FD and IBS where IBS had higher scores if the headache was determining variable. Both functional gastrointestinal disorders probably induce morphological and functional brain alterations due to impaired metabolism of serotonin with extraintestinal manifestations but more different tests should be done as our future perspectives in this field of investigation.

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Table 1. Group comparisons by categorical parameters

Parameters			Group		Total	p
			FD	IBS		
Sex	Male	n (%)	49 (56.3)	38 (43.7)	87 (100)	0.122
	Female	n (%)	99 (46.5)	114 (53.5)	213 (100)	
Headache	Yes	n (%)	51 (57.3)	38 (42.7)	89 (100)	0.073
	No	n (%)	97 (46)	114 (54)	211 (100)	
Globus	Yes	n (%)	63 (50.4)	62 (49.6)	125 (100)	0.755
	No	n (%)	85 (48.6)	90 (51.4)	175 (100)	
HD	None	n (%)	7 (43.8)	9 (56.3)	16 (100)	0.271
	Mild	n (%)	39 (47.6)	43 (52.4)	82 (100)	
	Moderate	n (%)	52 (44.8)	64 (55.2)	116 (100)	
	Heavy	n (%)	50 (58.1)	36 (41.9)	86 (100)	
HA	None	n (%)	9 (56.3)	7 (43.8)	16 (100)	0.949
	Mild	n (%)	75 (49.3)	77 (50.7)	152 (100)	
	Moderate	n (%)	22 (47.8)	24 (52.2)	46 (100)	
	Heavy	n (%)	42 (48.8)	44 (51.2)	86 (100)	
Total		n (%)	148 (49.3)	152 (50.7)	300 (100)	

Table 2. Group comparisons by score parameters

Parameters	Group				p
	FD		IBD		
	Median	IQR	Median	IQR	
Age	42.50	25	45	22	0.333
VAS Now	0	4	0	2	0.815
VAS Best	0	0	0	0	0.168
VAS Typical	0	5	0	4	0.170
VAS Worst	0	8	0	8	0.430
HD	21	13	21	9	0.242
HA	15.50	12	16	12	0.391

Table 3. Logistic regression, stepwise backward method, for Group predictions and determined parameters

Parameters	HR	95% CI LL	95% CI UL	p
VAS Best	1.438	1.042	1.985	**0.027**
HA	1.040	1.001	1.080	**0.043**
Headache (No)	3.307	1.599	6.839	**0.001**
Constant	0.186			0.005

Table 4. Determined Headache parameter and comparison of the parameters Sex and Groups

Headache				Group		Total	p
				FD	IBD		
Yes	Sex	Male	n (%)	27 (71.1)	11 (28.9)	38 (100)	**0.024**
		Female	n (%)	24 (47.1)	27 (52.9)	51 (100)	
	Total		n (%)	51 (57.3)	38 (42.7)	89 (100)	
No	Sex	Male	n (%)	22 (44.9)	27 (55.1)	49 (100)	0.863
		Female	n (%)	75 (46.3)	87 (53.7)	162 (100)	
	Total		n (%)	97 (46%	114 (54)	211 (100)	

Table 5. Determined Headache parameter and comparisons with parameters Score and Groups

Parameter	Group	Headache									
		Yes					No				
		N	Mean	Median	STD	p	N	Mean	Median	STD	p
Age	FD	51	41.41	33	15.478	0.549	97	44.61	43	13.610	0.557
	IBD	38	41.03	41.50	11.554		114	45.63	45	13.415	
VAS Now	FD	51	4.73	5	2.601	0.123	97	0.05	0	0.508	0.142
	IBD	38	5.18	6	2.415		114	0.29	0	1.480	
VAS Best	FD	51	0.63	0	1.183	**0.028**	97	0	0	0	0.191
	IBD	38	1.21	0	1.492		114	0.04	0	0.295	
VAS Typical	FD	51	6.06	6	1.580	0.943	97	0.12	0	0.869	0.351
	IBD	38	5.97	6	1.602		114	0.25	0	1.209	
VAS Worse	FD	51	8.47	8	1.206	**0.023**	97	0.27	0	1.517	0.423
	IBD	38	9.03	9	1.150		114	0.50	0	2.138	
HD	FD	51	28.61	28	4.976	0.656	97	16.74	17	5.553	0.748
	IBD	38	28.53	27	4.607		114	16.82	18	5.508	
HA	FD	51	26.61	30	8.139	0.403	97	15.70	15	4.895	**0.035**
	IBD	38	27.82	30	7.665		114	17.31	15	6.046	

Table 6. Logistic regression, stepwise backward method, by determining parameter Headache to identify prediction variables to identify the groups

Headache	Parameters	HR	95% CI LL	95% CI UL	p
Yes	Sex (male)	0.253	0.089	0.718	**0.010**
	VAS Best	1.410	0.984	2.020	0.061
	VAS Typical	0.577	0.377	0.884	**0.011**
	VAS Worse	2.191	1.273	3.771	**0.005**
	Constant	0.028			0.055
No	HA	1.092	1.022	1.166	**0.009**
	Constant	0.613			0.402

