Ashdin Publishing
Journal of Drug and Alcohol Research
Vol. 10 (2021), Article ID 236138, 7 pages

Research Article

From Ace 2 to Brain: Patterns, Correlations, Severity and Diversity of COVID-19 Symptoms among a Cohort of Patients

Muamar M. A. Shaheen* **and Manar A. J. Al-Junaidi**

Department of Clinical Pharmacy, Hebron University, Palestine

**Address Correspondence to Muamar M. A. Shaheen, muamarsh@hebron.edu*

Received October 07, 2021; Accepted October 21, 2021; Published October 28, 2021

Abstract

Background: Angiotensin II enzyme (ACE 2) was extensively investigated in SARS-CoV-2 as the viral entrance. The abundance, distribution and diversity of this enzyme dictate the wide range of symptoms patients suffer from during the acute phase of COVID-19 infection and determine late phase symptoms.

Objective: To determine factors associated with diversity of COVID-19 symptoms and relationship of these symptoms to each other.

Design and methods: This is a retrospective cohort study that involved 191 Polymerase Chain Reaction (PCR) positive COVID-19 patients who were symptomatic while home quarantined between March 2020 and January 2021 in Hebron district, southern West Bank. A well prepared questionnaire was used to gather clinical data and information about symptoms patients suffered from during the acute phase of infection.

Results: 191 symptomatic PCR positive COVID-19 subjects were included in this study. They were 31.4 ± 16.4 years old and 59.2% females. Using Fisher`s exact test, there was a strong relationship between anorexia and loss of either taste, smell, or both or not losing any of them, p=0.002. Suffering from Gastrointestinal (GIT) symptoms; such as diarrhea, nausea, vomiting, or combination of them was associated with anorexia, p=0.002. We found a significant relationship between specific GIT symptoms and dizziness, or headache; p=0.00, for each one.

There was a strong relationship between having any of the GIT symptoms and agues, or headache, p=0.045 and 0.000, respectively, on Pearson Chi-square test. There was also a relationship between gender and headache, p=0.002.

Conclusion: Local or systemic GI symptoms, neurological symptoms (headache, dizziness) along with smell and taste are connected to each other via gut brain axis or micro biota gut brain axis.

Keywords: Anorexia; Ageusia; Anosmia; Microbiota; Gut brain axis stewardship

Introduction

From the appearance of Corona virus in Wuhan, China and then to the rest of the world, many issues were arisen to be investigated. The nature of the virus, symptoms diversity and severity such as; fever, dry cough, dyspnea, headache, anosmia, dysgeusia, pneumonia, or even death are still poorly understood while some patients are remaining asymptomatic [1].

COVID-19, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third human coronavirus known to co-opt the peptidase angiotensin converting enzyme 2 (ACE 2) for cell entry. As with all coronaviruses, SARS-CoV-2 cell entry is dependent on its 180 kDa spike (S) protein, which mediates two essential events; binding to ACE 2 by the amino terminal region, and fusion of viral and cellular membranes through the carboxyl terminal region [2]. Other studies focused on the role and mechanisms of ACE 2, the effect on specific senses, and the role of some antihypertensive drugs that inhibit angiotensin converting enzyme that affect taste in these patients [3-7].

Trans membrane protease serine type 2 (TMPRSS2), type II trans membrane serine protease family, could cleave the coronavirus spike (S) protein. Studies have shown that ACE 2 and TMPRSS2 are not only expressed in lung tissues, but also in extra pulmonary organs including heart, kidney, liver, colon, esophagus, brain, gallbladder and testis, suggesting that SARS-CoV-2 may also affect extra pulmonary organs [8]. This explains the clinical problems related to these organs in COVID-19 patients; such as acute cardiac injury, abnormal liver functions in severe cases, and kidney damage. It also leads to heterogeneous symptoms, in terms of severity and diversity, according to different factors and involvement of different body organs. For example, some COVID-19 patients presented with gastrointestinal symptoms such as diarrhea, nausea, vomiting and abdominal pain along with symptoms from nervous system which could be diverse and complex. Olfactory and gustatory disorders are prevalent peripheral nervous system (PNS) symptoms, in mild and moderate COVID-19 patients and appeared prior to the other symptoms in some cases [8].

Recent evidence suggested that SARS-CoV-2 uses the ACE 2 receptor for cell entry, in synergy with the host's TMPRSS2. More specifically, the viral S glycoprotein is cleaved by TMPRSS2, thus facilitating viral activation and representing one of the essential host factors for SARS-CoV-2 pathogenicity [9]. Non-specific symptoms including headache, dizziness, vertigo, and paresthesia have also been reported. The most frequent one is anosmia. Some patients have developed respiratory symptoms several days (median, 1–2 days) after the emergence of non-specific neurological symptoms, including headache and dizziness. Lymphocytopenia has been associated with the more severe central nervous system symptoms, including acute stroke, intracerebral hemorrhage, seizure, and encephalitis [10].

Different studies categorized symptoms according to severity and stage. In one study, more than one third of patients experienced different neurological symptoms. These symptoms involve the central nervous system and lead to dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and epilepsy. Other symptoms such as taste, smell, and vision impairment, and neuralgia involve the peripheral nervous system, whereas some patients suffered of skeletal muscular damage [11]. Another study divided neurological symptoms into different stages based on severity; mild (headache, dizziness, disturbances of the state of consciousness), moderate (ataxia, epileptic manifestations, and stroke) and severe (hypo-aguesia, hyposmia, neuralgia) [12]. Other studies indicated the importance of headache as main symptom of COVID-19 with different characteristics and connection to pleocytosis [13-15]. One study indicated impaired consciousness in severe or critical cases of disease course [16].

Many suggested mechanisms for these symptoms depend mostly on the presence of the viral entrance (ACE 2) in certain tissues. GIT symptoms and some neurological ones are related together. Disturbances of gut microbial flora may be a factor behind the CNS symptoms like confusion and delirium which bonds ACE 2, CNS, and GIT symptoms together. This study also indicated that presence of nucleic acid of SARS-CoV-2 in fecal specimens may indicate the potentiality of the GIT in the transmission [17].

In this study, we are trying to find observational evidence augmented by statistical and epidemiologic data in order to elucidate the mechanisms of and interrelationships between these symptoms.

Materials and Methods

This is a retrospective cohort study that involved 191 Polymerase Chain Reaction (PCR) positive COVID-19 patients who were symptomatic. A well prepared questionnaire was used to gather clinical data and information about symptoms patients suffered from during the acute phase of infection. We assessed the presence or absence of symptoms by directly asking patients about their symptoms. We didn`t estimate severity neither stage of symptoms except for headache.

Results

A convenient sample consisting of 191 PCR positive COVID-19 subjects was included in this study. They were 31.4 ± 16.4 years old. Females form 59.2% of the sample. They were chosen depending on two criteria; PCR test and appearance of symptoms during the acute phase of infection. They were interviewed on the phone or using one of the social media applications. Sociodemographic characteristics and clinical data of our sample are included in Table 1. In Table 2 using Fisher`s exact test, there was a strong relationship between anorexia and loss of either taste, smell, or both or not losing any of them among patients, p=0.002. We tested the relationship between local GIT symptoms such as diarrhea, Nausea, vomiting or other GIT symptoms and loss of appetite. We discovered that people who suffered from any of these symptoms or combination of them are more prone to have anorexia compared to those who suffered none, p=0.002. We also found a significant relationship between some specific GIT symptoms and dizziness, p=0.00 and GIT specific symptoms and headache, p=0.00, (Table 3).

Table 1: Socio-demographic and clinical characters of participants

Variable	Count (percent) Mean ± STD Deviation
Age	31.406 ± 16.39
Gender	
Male	78 (40.8)
Female	113 (59.2)
BMI	27.09 ± 21.98
Blood Group	
A	72 (37.7)
B	33 (17.7)
AB	20 (10.5)
O	52 (27.2)
Chronic disease	
Yes	37 (19.4)
No	152 (79.6)
Career	
Teacher	15 (7.9)
Students	72 (37.7)
Private business	22 (11.5)
Not employed	42 (22)
Employee	30 (15.7)
Health care profession	8 (4.2)
Smoking	
Yes	30 (15.7)
No	160 (83.8)
Weight loss during the infection (14 days)	1.73 ± 2.708
Herbal use	
Yes	124 (64.9)
No	58 (30.4)
Using azithromycin	
Yes	89 (46.6)
No	90 (47.1)

Table 2: Relationship between loss of appetite and ageusia, anosmia or both during COVID-19 infection

Anorexia	Loss of smell and taste					Test value	sig
	Didn't lose any of them	Ageusia	Anosmia	Loss both senses	Total		
Yes	*21(38.2)	7(87.5)	12(63.2)	68(64.8)	108(57.8)	13.527	.002[b]
No	34(61.8)	1(12.5)	7(36.8)	37(35.2)	79(42.2)		
Total	55(100)	8(100)	19(100)	105(100)	187(100)		
Fisher's exact test *Numbers represent: Count (percent).							

Table 3: Relationship between anorexia (loss of appetite) and either dizziness or headache during COVID-19 infection and GIT symptoms.

Anorexia	Diarrhea (D)	Vomiting (V)	Nausea (N)	DVN + Abd. Pain*	No symptoms	[l]Others	total	Test value	sig
Yes	λ23(59)	3(60)	5(71.4)	17(81)	40 (44)	21(80.8)	109(58)	17.545	0.002[b]
No	16(41)	2(40)	2(28.6)	4(19)	50 (55.6)	5(19.2)	79(42)		
Total	39(10)	5(100)	7 (100)	21(100)	90(100)	26(100)	188(100)		
Dizziness								26.212	000b
Yes	22(56.4)	3(60)	5(71.4)	17(81)	27(30.7)	16(66.7)	90(48.9)		
No	17(43.6)	2(40)	2(28.6)	4(19)	61(69.3)	8(33.3)	94(51.1)		
Total	39(100)	5(100)	7(100)	21(100)	88(100)	24(100)	184(100)		
Headache								31.537	000[b]
Yes	33(84.6)	3(60)	7(100)	21(100)	55(61.1)	22(100)	141(76.6)		
No	6(15.4)	2(40)	0(00)	0(00)	35(38.9)	0(00)	43(23.4)		
Total	39(100)	5(100)	7(100)	21(100)	90(100)	22(100)	184(100)		
All done by Fischer's Exact test. λ Numbers represent: count (percent). *Having diarrhea, vomiting, nausea, and abdominal pain. [l] Others: constipation, Nausea and Vomiting, Nausea, vomiting & abdominal pain, or Diarrhea and abdominal pain.									

We also used McGill university scale for headache severity for all patients where we found that; 34.1% of the 183 subjects, who responded to this question, had headache severity from 8-10. Others have headache severity range from 0-7, data are not shown. We could not find a significant relationship between severity of headache and other symptoms.

GIT symptoms might be blurred for many patients. They might express GIT symptoms in a non-specific neither a precise way. They might also mix symptoms of GIT with other sensorineural symptoms or with each other. So we asked separate questions about GIT symptoms or other central or peripheral nervous system symptoms and distinct senses to make sure patients weren`t confusing anorexia for example with aguesia. We found a strong relationship between having any of the GIT symptoms and aguesia, or headache, p=0.045 and 0.000, respectively on Pearson Chi-square test (Table 4). On Pearson Chi-square test, there was also a relationship between gender and headache, with more affected females, p=0.002.

Table 4: Relationship between presence of one or more of GIT symptoms (vomiting, diarrhea, nausea, abdominal pain) and either ageusia or headache

Ageusia	Presence of GIT symptoms		Total	Test value	Sig.
	Yes	No			
Yes	62(68.9)	49(54.4)	111(61.7)	3.972[a]	0.046
No	28(31.1)	41(45.6)	69(38.3)		
Total	90(100)	90(100)	180(100)		
Headache				22.630[a]	0.00
Yes	83(91.2)	55(61.1)	138(76.2)		
No	8(8.8)	35(38.9)	43(23.8)		
Total	91(100)	90(100)	181(100)		

Discussion

COVID-19 patients suffered from a wide range of symptoms. In depth pathogenic analysis for some of these symptoms, lead to potential conclusion that ACE 2 viral entrance expression and inter individual variability play a major role in symptom diversity and severity among patients. Trans

membrane protease serine type 2 (TMPRSS2) also buffered the extent to which the S spike protein of the virus might invade any organ depends, most of the time, on the differential expression of this enzyme receptor on the cell surface of these cells and tissues. Not only the availability of these receptors, but also the readiness of the immune system to present the spike protein, will by default make this hypothesis valid and dictate the symptoms diversity and severity.

As with other flu viruses, historically losing smell and taste lead to reduction in appetite. In our study, we found a strong relationship between anorexia and losing one or the other or losing both senses (taste and smell). Losing both senses was the most prevalent case and the most predictor of losing appetite. In the same table, many patients didn`t lose any of these senses neither did they suffer from loss of appetite during the acute phase of the infection. At the same side, 37 patients have lost both senses, yet have not lost their appetite. This could be explained by the suggestion that ACE 2 receptor distribution in gut and taste buds might be widely different among patients. This phenomenon could be explained in 2 ways; some studies reported high ACE 2 expression on the oral cavity mucosa and the epithelial cells of the tongue. As such, SARS-CoV-2 may have an effect on the taste buds or receptors directly in addition to the direct effect of the virus on ACE 2 of GIT, both having the entrance of the virus, so they are related together.

There are wide differences among patients in regard to expression and distribution of ACE 2 enzyme. This explains the heterogonous intensity of the viral symptoms patients suffered from, especially those symptoms that are related to the direct effect of the virus, in addition to the differences in immunity response and antigen presenting abilities as indicated earlier in the introduction. Second, GIT upset will disturb normal flora that will produce more toxins to brain which will lead to confusion and appetite disturbances in predisposed patients who have high receptor density of ACE 2 in their gut. So no wonder you might lose taste and smell without losing appetite if you don`t have enough receptors in their GIT or the virus didn`t occupy these receptors.

These findings match a study that concluded presence of COVID-19 virus in intestinal tissues resulted in GI symptoms, such as diarrhea and abdominal pain. Metabolic disorders increase the absorption of harmful metabolites, which will affect the function of the central nervous system through the gut brain axis, leading to dizziness and fatigue. Disorders of intestinal metabolism further lead to more harmful metabolites that are harmful to liver tissue [18].

Plethora of studies focused on the inter correlations between smell, taste and appetite concluded that losing one or more of these senses affect the priming role of eating behavior, satiety, and energy intake. These studies emphasize the importance of the orthonasal exposure for odor and recognizing and memorizing flavor of food or shifting focus towards the texture of food in time of chemosensory dysfunction in order to maintain consumption [19-23]. This proves valid the previous results we reached at that loosing taste and/or smell might not necessarily lead to anorexia since body shift to other mechanisms to prime eating. Furthermore, we studied the relationship between GI symptoms and other COVID-19 symptoms in order to clear any confusion between these symptoms patients might fall in during the interview. We found 40 patients suffered of anorexia without suffering of any GI symptoms, 59 patients suffered from loss of appetite who expressed one or more GI symptoms and 23 patients suffered mainly of diarrhea as main GI symptom and loss of appetite.

In this context, a study found that, the brain gut axis represents a complex bi-directional system comprising multiple interconnections between the neuroendocrine pathways, the autonomous nervous system and the gastrointestinal tract. Once the virus entry disturbs this precise balance among these three systems, many symptoms might appear including loss of appetite [24]. Disturbing the microbiota, in the GIT system, as one of the key regulators of gut brain function has led to the appreciation of the importance of a distinct microbiota gut brain axis and ultimately leads to variety of COVID-19 symptoms. The microbiota and the brain communicate with each other via various routes including the immune system, tryptophan metabolism, the vagus nerve and the enteric nervous system.

A study found that the gut microbiota is critically important for the appropriate development and maintenance of brain function. This lead to the expansion of the Gut Brain Axis concept into Microbiota Gut Brain Axis or Diet Microbiota Gut Brain Axis [25].

Intact intestinal microbiota is crucial for preventing and decreasing COVID-19 complications. Another study revealed the important role of ACE 2 expression on the small intestine surface cells that can mediate viral invasion and expansion, triggering gastrointestinal inflammation. SARS-CoV-2 invades intestinal cells expressing ACE 2, causing malabsorption, intestinal disorders, activation of the enteric nervous system, and, ultimately, diarrhea [26]. Diarrhea, for example, most prevalent GI symptom in our sample, was associated with loss of appetite.

Another study stressed the precious role of the vagus nerve in regulation of appetite, mood, and inflammation. This nerve is important in coordinating the complex interactions between central and peripheral neural control mechanisms for appetite, mood, and intestinal inflammation [27].

Having this said, we can interpret the relationship between dizziness and GI symptoms among our patients depending on the gut brain axis mentioned above where metabolic disorders that increase the absorption of harmful metabolites affect the function of the central nervous system leading to dizziness and fatigue, as explained above.

On the other hand headache could be explained in 2 postulated observations from previous clinical studies. These studies found that frequency, duration and/or intensity of migraine events were reduced with probiotic administration as explained earlier. The microbiota gut brain axis. Physiological reviews. It is well known from the previ-

ous discussion that COVID-19 disturbs the microbiota gut brain axis integrity and function which could lead to different levels of headaches as pointed out using McGill scale in our study.

Second explanation; one study found higher levels of IL-10 in the sera of patients with headaches who showed intense immune response. IL-10 counteracts cytokine release in these patients. This implies that patients who suffered of headache might have more severe cases of the COVID-19 infection and went through cytokine storm [28]. We didn`t study these factors among our patients due to the retrospective nature of our study, henceforth, we can`t judge on any of these mechanisms. Yet both explanations are highly possible.

Females were more susceptibility to headaches than males in our study. This is well known in literature the sensitivity of females to headache and it comes along with Celentano, D study about headache in COVID-19 and gender [29].

When it comes to aguesia and GI symptoms; 62 patients of our sample suffered of GI symptoms along with aguesia, and 28 patients had aguesia without GI symptoms.

Two possible mechanisms for this observation first explanation: on the basis of availability and differential expression of ACE 2 enzymes on the mucosa of oral cavity and epithelial cells of the tongue has been explained above. Some studies reported high expression of ACE 2 enzymes in these areas; hence, these individuals will suffer of aguesia regardless of GI symptoms. On the other hand individuals who showed both GI symptoms and aguesia may have expressed high levels of the enzyme in both areas (GIT wall and mouth). In short, SARS-CoV-2 may have an effect on the taste buds or receptors directly in addition to its direct effect on ACE 2 in the GIT, both having the entrance of the virus. This explains the intra and inters individual differences in experiencing some of the symptoms, but it doesn't take into consideration the effect of severity of COVID-19 infection or the immune system response on symptoms intensity and/or diversity.

This takes us to the second possible explanation. It was found that patients who suffered severe COVID-19 infection who might have cytokine storm (with systemic or local production of IL-6), along with viral replication in the GI wall that lead to tissues damage, might suffer of GI complications. Through the vagus nerve pathway, these cytokines promote nausea, vomiting, and diarrhea in complicated cases of COVID-19 infections.

Conclusion

COVID-19 symptoms though constitute a diverse group of symptoms in term of intensity and diversity, intra and inter individual, can be explained on the basis of genetic expression of ACE 2 enzyme. These symptoms can be correlated to each other using the (microbiota) gut brain axis pathway

Ethics Approval

This research was approved by the IRB board at Hebron University. We took a verbal consent, due to the pandemic situation, from all participants to voluntarily participate in this study.

Conflict of Interest

The authors declare that they have no potential competing interests.

Acknowledgment

The authors would like to acknowledge Wollo University College of Medicine and Health Sciences, Department of Pharmacy

References

1. J. F. M. Almeida, E. Z. Chehte, COVID-19 and the gastrointestinal tract: What do we already know?, Einstein (Sao Paulo), 18 (2020), eRW5909.
2. N. J. Matheson, P. J. Lehner, How does SARS-CoV-2 cause COVID-19?, Science, 369 (2020), 510-511.
3. A. Bigiani, Gustatory dysfunctions in COVID-19 patients: Possible involvement of taste renin-angiotensin system (RAS), Eur Arch Otorhinolaryngol, 277 (2020), 2395.
4. N. Shigemura. Angiotensin II and taste sensitivity, Jpn Dent Sci Rev, 51 (2015), 51-58.
5. Y. Zhao, Z. Zhao, Y. Wang, Y. Zhou, Y. Ma, et al. Single-Cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2, Am J Respir Crit Care Med, 202 (2020), 756-759.
6. W. Ni, X. Yang, D. Yang, J. Bao, R. Li, et al., Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19, Crit Care, 24 (2020), 422.
7. J. Sulibursk, G. Duda, D. Pupek-Musialik, The influence of hypotensive drugs on the taste sensitivity in patients with primary hypertension, Acta Pol Pharm, 69 (2012), 121-7.
8. M. Dong, J. Zhang, X. Ma, J. Tan, L. Chen, et al. ACE2, TMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19, Biomed Pharmacother, 131 (2020), 110678.
9. V. Mollica, A. Rizzo, F. Massari. The pivotal role of TMPRSS2 in coronavirus disease 2019 and prostate cancer, Future Oncol, 16 (2020), 2029-2033.
10. J. Kanjanaumporn, S. Aeumjaturapat, K. Snidvongs, K. Seresirikachorn, S. Chusakul. Smell and taste dysfunction in patients with SARS-CoV-2 infection: A review of epidemiology, pathogenesis, prognosis, and treatment options, Asian Pac J Allergy Immunol, 38 (2020), 69-77.
11. S. Drożdżal, J. Rosik, K. Lechowicz, F. Machaj, B. Szostak, et al. COVID-19: Pain Management in Patients with SARS-CoV-2 Infection-Molecular Mechanisms, Challenges, and Perspectives, Brain Sci, 20 (2020), 465.
12. S. Jamwal, A. Gautam, J. Elsworth, M. Kumar, Chawla

R, et al. An updated insight into the molecular pathogenesis, secondary complications and potential therapeutics of COVID-19 pandemic, Life Sci, 15 (2020), 118105.

13. G. Lippi, C. Mattiuzzi, C. Bovo, B. M. Henry. Headache is an important symptom in patients with coronavirus disease 2019 (COVID-19), Diagnosis (Berl), 7 (2020), 409-411.
14. Ö. Uygun, M. Ertaş, E. Ekizoğlu, H. Bolay, A. Özge, et al. Headache characteristics in COVID-19 pandemic-a survey study, J Headache Pain, 21 (2020), 121.
15. F. A. A. Oliveira, D. C. C. Palmeira, P. A. S Rocha-Filho, Headache and Pleocytosis in CSF associated with COVID-19: Case report, Neurol Sci, 41 (2020), 3021-3022.
16. X. Chen, S. Laurent, O. A. Onur, N. N. Kleineberg, G. R. Fink, et al. A Systematic review of neurological symptoms and complications of COVID-19, J Neurol, 268 (2021), 392-402.
17. Y. Song, P. Liu, X. L. Shi, Y.L. Chu, J. Zhang, et al. SARS-CoV-2 induced diarrhea as onset symptom in patient with COVID-19, Gut, 69 (2020), 1143-1144.
18. Z. Zhou, N. Zhao, Y. Shu, S. Han, B. Chen. Effect of Gastrointestinal Symptoms in Patients With COVID-19, Gastroenterology, 158 (2020), 2294-2297.
19. T. Li, M. Zhao, A. Raza, J. Guo, T. He, et al., The effect of taste and taste perception on satiation/satiety: a review, Food Funct, 11 (2020), 2838-2847.
20. S. Boesveldt, K. Graaf, The Differential Role of Smell and Taste For Eating Behavior, Perception, 46 (2017), 307-319.
21. A. T. Z. B. Høier, N. Chaaban, B. V. Andersen, Possibilities for Maintaining Appetite in Recovering COVID-19 Patients, Foods, 20 (2021), 464.
22. E. Mehraeen, F. Behnezhad, M. A. Salehi, T. Noori, H. Harandi, et al., Olfactory and gustatory dysfunctions due to the coronavirus disease (COVID-19): A review of current evidence, Eur Arch Otorhinolaryngol, 278 (2021), 307-312.
23. A. Y. Han, L. Mukdad, J. L. Long, I. A. Lopez. Anosmia in COVID-19: Mechanisms and Significance, Chem Senses, 17 (2020), bjaa040.
24. S. Peppas, C. Pansieri, D. Piovani, S. Danese, L. Peyrin-Biroulet, et al., The Brain-Gut Axis: Psychological Functioning and Inflammatory Bowel Diseases, J Clin Med, 20 (2021) 377.
25. J. F. Cryan, K.J. O'Riordan, C. S. M. Cowan, K. V. Sandhu, T. F. S. Bastiaanssen, et al. The Microbio- ta-Gut-Brain Axis, Physiol Rev, 99 (2019), 1877-2013.
26. H. Y. Lei, Y. H. Ding, K. Nie, Y.M. Dong, J. H. Xu, et al. Potential effects of SARS-CoV-2 on the gastrointestinal tract and liver, Biomed Pharmacother, 133 (2021), 111064.
27. K. N. Browning, S. Verheijden, G. E. Boeckxstaens, The Vagus Nerve in Appetite Regulation, Mood, and Intestinal Inflammation, Gastroenterology, 152 (2017), 730-744.
28. J. Trigo, D. García-Azorín, Á. Sierra-Mencía, Á. Tamayo-Velasco, P. Martínez-Paz, et al, Cytokine and interleukin profile in patients with headache and COVID-19: A pilot, CASE-control, study on 104 patients, J Headache Pain, 22 (2021), 51.
29. D. D. Celentano, M. S. Linet, W. F. Stewart, Gender differences in the experience of headache, Soc Sci Med. 30 (1990), 1289-95.