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Research Paper

Evaluation of the Relationship Between Celiac Disease and Refractory Epilepsy in Patients Referring to Imam Khomeini Hospital, Urmia

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ABSTRACT

Introduction: Celiac disease can be associated with other diseases, including neurological disorders. In this study, the relationship between celiac disease and refractory epilepsy was evaluated in patients who were referred to Imam Khomeini Hospital in Urmia.

Methods: In this cross-sectional study, patients with refractory epilepsy who were referred to the neurology clinic of Imam Khomeini Hospital in Urmia, during the second half of 2019 and cases with controlled epilepsy were studied as a control group. The statistical population of the present study included 50 patients with refractory seizures and 50 patients with controlled seizures. The mean age of patients was 32.96±11.35 years. Five milliliters of blood samples were taken from the patients, and a serum anti-tTG test was performed using the ELISA kit. Then, in patients with positive anti-tTG, a duodenal biopsy sample was prepared using an endoscopy.

Results: This study showed that the mean serum level of anti-tTG in patients with refractory epilepsy was higher than in patients with controlled epilepsy. Anti-tTG test results were positive in five out of 50 patients with refractory epilepsy, and it was positive in two out of 50 patients with controlled epilepsy. There was no significant difference between the two groups in terms of serum levels of anti-tTG (P=0.14). Also, there was no significant relationship between serum levels of anti-tTG, age, and genus (P>0.05). Biopsy results in three patients in the refractory epilepsy group and one patient in the controlled epilepsy group were in favor of a definitive diagnosis of celiac disease. Patients with confirmed celiac disease using endoscopy had higher anti-tTG levels (P=0.006).

Conclusion: There was no significant difference between celiac disease in cases with refractory epilepsy and controlled epilepsy.

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Highlights

- Celiac disease can be associated neurological disorders.
- Mean serum level of anti-tTG in refractory epilepsy patients was higher of controlled epilepsy.
- There was no significant relationship between celiac disease in cases with refractory epilepsy.

Plain Language Summary

Celiac disease is an autoimmune disease that occurs in genetically predisposed people as a result of eating foods containing gluten. Celiac disease can be associated with other diseases, such as neurological diseases, liver, endocrine, bone metabolism, etc. The prevalence of the celiac disease among patients with epilepsy has been reported in the range of 0.5-1 %. Screening is very important to prevent long-term complications of celiac disease. Furthermore, a gluten-free diet has been suggested as having a protective role in autoimmune disorders and epilepsy control. According to the results of the study, the relationship between celiac disease and refractory epilepsy in adult patients was not proved; therefore, using a gluten-free diet has no effect on the ability to control epilepsy, particularly in refractory cases.

1. Introduction

Celiac disease or gluten-sensitive anthropopathy is an autoimmune disorder. In people genetically predisposed to celiac disease, eating gluten, which is part of the structure of many celebs, can lead to intestinal tract damage with an inadequate immune response (Gujral et al., 2012). In this disease, the intestinal villi are destroyed, and the intestinal absorption capacity is reduced. The disease has various clinical manifestations and can occur at any age, despite the prevalence of the disease in childhood and adolescence, and even adulthood, about 20 % of patients are over 60 years old at the time of diagnosis (Gatti et al., 2020). The cause of the disease is gluten. Gluten is a general term for a group of water-insoluble proteins that are given different names in different grains. People genetically predisposed to DQ2, the less common DQ8 human leukocyte antigen, are more susceptible to the disease (Balakireva et al., 2016; Caio et al., 2019).

The prevalence of the disease in epidemiological estimates is lower than the actual prevalence. The highest prevalence of the disease has been reported in Western Europe. For example, its prevalence in Scandinavia is 1.99 %. Recent studies have indicated that the prevalence of celiac disease in the United States is comparable to that in Western Europe (Xia et al., 2020; Masood et al., 2020; Rostami et al., 2011). The four diagnostic criteria are malabsorption due to gluten consumption in wheat and barley, atrophy of the small intestinal mucosa, the improvement of clinical symptoms of malabsorption with the improvement of atrophic symptoms of the small intestine by cutting gluten-containing foods, and recurrence of clinical and histological symptoms after restarting gluten-containing foods (Rubio-Tapia et al., 2013; Rozenberg et al., 2020). Serological tests and small bowel biopsies are the most accurate diagnostic tests for celiac disease. To diagnose this disease, the initial evaluation is performed using serological tests. When a serological test is positive, a small bowel biopsy should be done to confirm the disease (Kelly et al.,2015). Among the serological diagnostic tests in celiac disease, the anti-tTG IgA test and endomysial Ab (EMA) assay can be mentioned. Anti-IgA tests are one of the most useful and best tests, with high sensitivity and specificity in the diagnosis of celiac disease, and provide the possibility of screening for the disease (Schyum et al., 2013).

Anti-tTG antibodies can be easily measured by ELISA. Today, screening for celiac disease by anti-tTG is recommended. Because EMA-IgA is a more expensive method, it is more complicated. On the other hand, tTG-IgA was able to identify all cases of false-negative EMA-IgA. Celiac disease can be associated with other diseases, such as herpetic dermatitis, neurological diseases, liver, endocrine, bone metabolism, etc. (Sobhani et al., 2020). The most common neurological disorders are headaches, epilepsy, cerebellar ataxia, and polyneuropathy. The relationship between epilepsy and celiac disease has been discussed in various studies. The prevalence of the celiac disease among patients with epilepsy has been reported in the range of 0.5-1 %. Screening is very important to prevent long-term complications of celiac disease. Furthermore, a gluten-free diet has

been suggested as having a protective role in autoimmune disorders and epilepsy control (Taraghikhah et al., 2020). Because different neurological disorders, such as headache, cerebellar ataxia, and epilepsy have been reported in patients with celiac disease and the prevalence of celiac disease in these patients with epilepsy is different in more studies, celiac screening in patients with epilepsy can reduce long-term complications. Also, due to the lack of a similar study in the country, this study was done to investigate the relationship between celiac disease and refractory epilepsy in patients who were referred to Imam Khomeini Hospital in Urmia.

2. Materials and Methods

In this cross-sectional study, patients with refractory epilepsy who were referred to the neurology clinic of Imam Khomeini Hospital in Urmia during the second half of 2019 and cases with controlled epilepsy were studied as a control group. Resistant epilepsy was defined as uncontrolled epilepsy despite treatment with two drugs, with an appropriate dose for six months. The present study obtained permission from the Ethics Committee of East Azerbaijan University of Medical Sciences and the management of Imam Khomeini Hospital in Urmia. After completing the written consent form for the patients participating in the study, 5 ml of blood samples were taken from them, and the serum levels of tissue transglutaminase (anti-tTG) IgA were assessed using the ELISA test. Then, if the test was positive in patients, a duodenal biopsy specimen was prepared using endoscopy and the biopsy specimen was examined by a pathologist without knowing the serological results and using Marsh criteria (Table 1).

Inclusion criteria

Patients older than 18 years with refractory epilepsy and resistant epilepsy defined as uncontrolled epilepsy despite treatment with two drugs and appropriate doses for six months were inclusion criteria.

Exclusion criteria

Exclusion criteria included structural disorders of the brain and electrolyte disorders.

Measurement of anti-tTG serum levels

After blood sampling, centrifugation and separation of serum were done and it was transferred to two vials immediately and kept at negative temperatures. Serum levels of tissue IgA tran-glutaminase (anti-tTG) were assessed using ELISA and recombinant human anti-tTG was used as the antigen (AU-tTG IgA, Erospital, Trieste, Italy). According to the manual of the kit, values of more than seven international units/ml were considered positive.

Duodenal biopsy

The tissue view of small bowel biopsy in people with celiac disease has special morphological characteristics. Typically, the inner surface of the intestine has villi. In people with celiac disease, this condition disappears and the intestinal surface becomes smooth. Histological changes are made to diagnose celiac disease based on marsh classification definitively. In marsh I, the normal appearance of the mucosa is seen with an increase in lymphocytes within the epithelium of the villi. Marsh III is also seen with hyperplastic crypts and moderate to severe reduction of villi. Most patients with celiac disease at the time of diagnosis fall into the marsh III category. Marsh III is also based on the severity of the conflict in three classes of IIIa, IIIb, and IIIc; in marsh IIIa you have a relative atrophy of the villi so that the ratio of the villus to the crypt is less than three to one. In marsh IIIb, we have subtotal villous atrophy and in marsh IIIc, we have atrophy of the complete villi so that the small intestinal mucosa is completely similar to the colon mucosa. If the pathology is consistent with celiac disease, a definitive diagnosis of celiac disease is made.

Specifications of data collection tools and how to collect it

Blood (5 ml)was taken from the atients participating in the study at the beginning of the study to assess serum anti-tTG levels. If the antibody was positive, they were asked to refer to a duodenal mucosa sample.

Statistical analysis of data

After collecting information, the data were entered into SPSS 21 and statistically analyzed. Then, the mean and standard deviation were used to describe the quantitative data, and tables and graphs were used for the qualitative data. The independent sample t-test (or its nonparametric equivalent) was used to compare quantitative variables in the two groups and a Chi-square test was used to compare qualitative variables in the two groups. If the distribution was abnormal, it was evaluated using the Spearman test, and a p-value level less than 0.05 was considered statistically significant.

Table 1. Biopsy Marsh criteria

Types	Definitions
0	Natural and normal biopsy
I	Normal appearance of mucosa with increased lymphocytes in mucosal epithelium
II	hyperplastic crypts and natural villi of the intestine
IIIa	hyperplastic crypts and relative atrophy of intestinal villi
IIIb	hyperplastic and almost complete atrophic crypts of intestinal villi
IIIc	hyperplastic crypts and complete atrophy of intestinal villi

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Ethical notes

At the beginning of the study, written consent was received from all patients. No fee was charged to patients for participating in the study and performing the necessary tests. In this study, the personal characteristics of the patients were not recorded in any written document. Also, the implementation stages of the project did not begin before receiving the code of ethics from the ethics committee of West Azerbaijan University of Medical Sciences.

Executive limitations of the plan and how to reduce them

One of the limitations of the present study is the possibility of patients' unwillingness to participate in the study. To address this issue, they were told that participating in the study would not be an unproven treatment for them, would not be harmful, and would not be costly.

3. Results

Demographic profile

The study was performed on 50 patients with refractory epilepsy and 50 patients with controlled epilepsy as a control group. The Mean±SD age of patients was 32.96±11.35 years. Independent t-test showed no significant difference between the two groups in terms of age (P=0.57). Genus distribution in the two groups was significant; in the group with refractory epilepsy, 46 % and in the group with controlled epilepsy, 62 % were women (P=0.001) (Table 2).

Evaluation of serum levels of tissue anti-transglutaminase (anti-tTG)

The serum levels of tissue anti-transglutaminase were assessed by the ELISA method. The mean serum levels of the anti-tTG in patients with refractory epilepsy were 4.6 AU / ml, and in the group with controlled epilepsy were 3.0 AU / ml (Figure 1). Anti-tTG test results were positive in five out of 50 patients with refractory epilepsy and in two out of 50 patients with controlled epilepsy. Independent t-test showed a statistically significant difference between them. There was no difference between the two groups in terms of serum anti-tTG levels (P=0.14) and no significant relationship was found between serum anti-tTG levels and age (P>0.05) and genus (P>0.05).

Pathological examination of duodenal biopsy

In patients with anti-tTG levels higher than 7 AU / ml, upper endoscopy and a duodenal biopsy were performed for pathological examination. Out of 50 patients with

Table 2. Demographic characteristics of patients

Demographic Variable		Resistant Epilepsy	Controlled Epilepsy	Sig.
Age, Mean±SD		32.30±1.54	33.60±1.67	0.57
Gender, %	Female	46	62	0.001
	Man	53	38	

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Table 3. Comparison of duodenal pathology in the group with refractory epilepsy and controlled epilepsy

Pathology of Duodenal Biopsy	No. (%)		Sig.
	Resistant Epilepsy	Controlled Epilepsy	
Positive	3(60)	1(50)	
Negative	2(40)	1(50)	0.74
Total	5(100)	2(100)	

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refractory epilepsy, the duodenal biopsy was performed in five patients, and out of 50 patients with controlled epilepsy, in two patients. The result of biopsy in three patients in the group resistant to epilepsy and one patient in the group with controlled epilepsy favored a definite celiac disease diagnosis. The Chi-square test showed that there was no statistically significant difference between the two groups in terms of involvement with celiac disease (P>0.05) (Table 3). The characteristics of four patients with duodenal biopsy in favor of a definitive diagnosis of celiac disease are described in Table 4.

In the present study, no significant relationship was found between the diagnosis of celiac disease and age, genus, and refractory epilepsy (P>0.05). The mean serum levels of anti-tTG in patients with pathological diagnosis of celiac disease were 50.5±11.42 AU/ml and in patients with the positive anti-tTG test were 11.16±1.76 AU/ml. A comparison of serum anti-tTG levels in patients with pathological diagnosis of celiac disease and other patients who underwent endoscopy by independent t-test showed that the levels of anti-tTG in patients with pathological diagnosis of celiac disease were significantly higher than other patients (P=0.006) (Figure 2).

4. Discussion

Analysis of the findings of the present study showed that the Mean±SD age of patients was 32.96±11.35 years. Genus distribution in the two groups was statistically significant. In the group with refractory epilepsy, 46 % and in the group with controlled epilepsy, 53 % were women (P=0.001). The mean serum levels of anti-tTG in patients with refractory epilepsy were 4.6 AU/ml, and 3.0 AU/ml in the group with controlled epilepsy. Anti-tTG test was positive in five patients with refractory epilepsy and positive in two out of 50 patients with controlled epilepsy. The independent t-test showed no statistically significant difference between the two groups in terms of serum anti-tTG levels (P=0.14). Also, no significant relationship was found between serum anti-tTG levels and age (P>0.05) and genus (P>0.05).

Biopsy in three patients in the refractory seizure group and one patient in the controlled seizure group favored a definitive diagnosis of celiac disease. Statistical tests also showed that there was no statistically significant difference between the two groups in terms of involvement with celiac disease (P>0.05). Also, comparing serum anti-tTG levels in patients with pathological diagnosis of celiac disease and other patients undergoing scapularity in independent t-test showed that anti-tTG levels in patients with pathological diagnosis of celiac disease were significantly higher than other patients (P=0.006). Karimzadeh et al. (2010) designed a cross-sectional study in 2020 in Tehran to investigate the relationship between celiac disease and refractory epilepsy. Therefore, 155 children with idiopathic epilepsy were included in the study. The results of this study showed

Table 4. Characteristics of 4 patients with duodenal biopsy in favor of a definitive diagnosis of celiac disease

Patient	Type of Seizure	Gender	Age	Ant-tTG (AU/ml)
1	Controlled	Women	33	22
2	Resistant to treatment	Man	19	45
3	Resistant to treatment	Women	53	59
4	Resistant to treatment	Women	28	76

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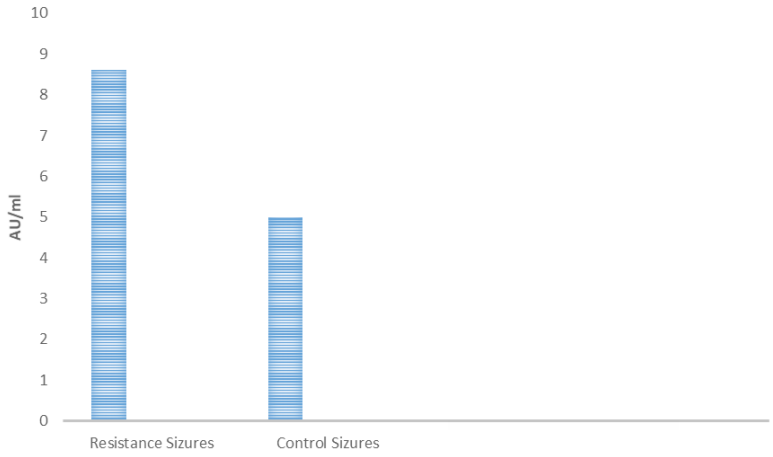

Figure 1. Serum levels of tissue anti-transglutaminase in two groups of refractory and control epilepsy

that the Mean±SD age of patients was 6.7±3.3 years. In our study, adult patients were included in the study and the Mean±SD age was 32.96±11.35 years. In the study by Karimzadeh et al., the levels of tTG antibody were positive in seven patients with epilepsy. A study by Dai et al. (2014) examining the prevalence of temporal lobe epilepsy and celiac disease also showed that out of 90 children, two patients were found with temporal lobe epilepsy (serum tTG).

A study by Vieira et al. (2013) found that out of 100 children with epilepsy, three had anti-tTG, and in a study by Mavroudi et al. on 255 children with epilepsy and 280 healthy children, anti-tTG positive was detected in five children with epilepsy. In our study, anti-tTG was positive in two out of 50 patients with controlled epilepsy. In the study by Karimzadeh et al., which was conducted to investigate the association between celiac disease and refractory tuberculosis, seven children were positive for anti-tTG and the biopsies of three of them were positive (Karimzadeh et al., 2010).

In the study by Dai et al., where the level of anti-tTG was high in two children, the pathological examination of the biopsy specimens also showed evidence of celiac disease in the biopsy specimens of these two children (Dai et al., 2014). A study by Vieira et al. found that out of 100 children with epilepsy, three had anti-tTG, with normal duodenal mucosa in two cases and lymphocytic infiltration in one case (Vieira et al., 2013). A study by Mavroudi et al. on 255 children with epilepsy and 280 healthy children showed that anti-tTG-positive was detected in five children with epilepsy. Histological changes were found in the biopsy of all five children with epilepsy (Mavroudi et al., 2007).

A study by Fois et al. (1993) in Italy showed that celiac antibodies were positive in nine children, and a biopsy confirmed the diagnosis of celiac disease (Fois

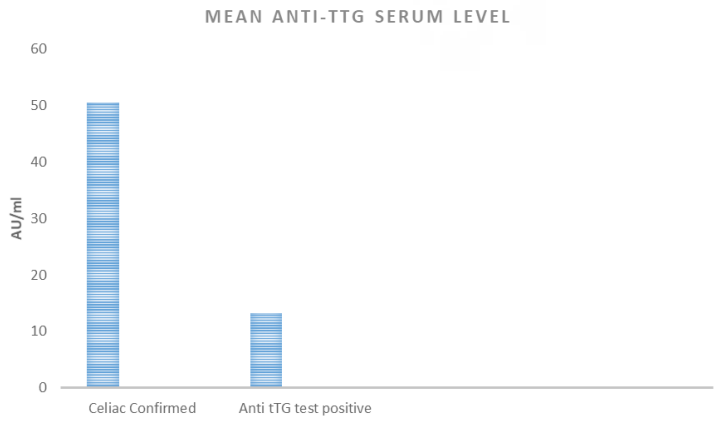

Figure 2. Mean serum anti-tTG levels in patients with pathological diagnosis of celiac disease and patients with a positive anti-tTG test.

et al., 1994). In our study, a biopsy of three patients in the refractory seizure group and one patient in the controlled seizure group favored a definitive diagnosis of celiac disease. The results of this study showed that the Mean±SD age of patients was 32.96 ±11.35 years. Genus distribution in the two groups was statistically significant. In comparison with the uncontrolled group, a higher percentage of the controlled group was women. Also, 46% in the group with refractory seizures and 53% in the group with controlled seizures were female (53 vs. 46%, P=0.001).

The mean serum levels of anti-tTG in patients with refractory epilepsy were higher than in patients with controlled epilepsy. Anti-tTG test was positive in five patients with refractory epilepsy and positive in two patients out of 50 patients with controlled epilepsy. There was no statistically significant difference between the two groups in terms of serum anti-tTG levels. No significant relationship was found between serum anti-tTG level and age and genus. Biopsy in three patients in the refractory seizure group and one patient in the controlled seizure group favored a definitive diagnosis of celiac disease. Also, there was no statistically significant difference between the two groups in terms of involvement with celiac disease. Compared with patients who had a positive anti-tTG level, the levels of anti-tTG were higher in patients who had a biopsy-confirmed disease (P=0.006).

5. Conclusion

According to the results of the study, the relationship between celiac disease and refractory epilepsy in adult patients was not proved; therefore, using a gluten-free diet has no effect on the ability to control epilepsy, particularly in refractory cases.

Ethical Considerations

Compliance with ethical guidelines

This study was executed under the supervision of the Ethics Committee of Urmia University of Medical Sciences, Urmia, Iran (No.: IR.UMSU.REC.1398.442).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declare no conflicts of interest.

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References

Balakireva, A. V., & Zamyatnin, A. A. (2016). Properties of gluten intolerance: Gluten structure, evolution, pathogenicity and detoxification capabilities. *Nutrients, 8*(10), 644. [DOI:10.3390/nu8100644] [PMID] [PMCID]

Caio, G., Volta, U., Sapone, A., Leffler, D. A., De Giorgio, R., & Catassi, C., et al. (2019). Celiac disease: A comprehensive current review. *BMC Medicine, 17*(1), 142. [DOI:10.1186/s12916-019-1380-z] [PMID] [PMCID]

Dai, A. I., Akcali, A., Varan, C., & Demiryürek, A. T. (2014). Prevalence of resistant occipital lobe epilepsy associated with celiac disease in children. *Child's Nervous System, 30*(6), 1091-1098. [DOI:10.1007/s00381-014-2387-6] [PMID]

Fois, A., Vascotto, M., Di Bartolo, R. M., & Di Marco, V. (1994). Celiac disease and epilepsy in pediatric patients. *Child's Nervous System : Chns : Official Journal of the International Society for Pediatric Neurosurgery, 10*(7), 450–454. [DOI:10.1007/BF00303610] [PMID]

Gatti, S., Lionetti, E., Balanzoni, L., Verma, A. K., Galeazzi, T., & Gesuita, R., et al. (2020). Increased prevalence of celiac disease in school-age children in Italy. *Clinical Gastroenterology and Hepatology, 18*(3), 596-603. [DOI:10.1016/j.cgh.2019.06.013] [PMID]

Gujral, N., Freeman, H. J., & Thomson, A. B. (2012). Celiac disease: Prevalence, diagnosis, pathogenesis and treatment. *World Journal of Gastroenterology: WJG, 18*(42), 6036–6059. [PMID] [PMCID]

Karimzadeh, P., Khajeh, A., Tabarestani, S., Imanzadeh, F., & Azargashb, E. (2010). Relationship between Celiac Disease and Refractory Idiopathic Epilepsy in Children. *Iranian Journal of Child Neurology, 4*(4), 19-24. [DOI:10.22037/ijcn.v4i4.2078]

Kelly, C. P., Bai, J. C., Liu, E., & Leffler, D. A. (2015). Advances in diagnosis and management of celiac disease. *Gastroenterology, 148*(6), 1175-1186. [PMID] [PMCID]

Masood, J., Rehman, H., Anjum, Z. M., Iqbal, I., Zafar, S., & Ayesha, H. (2020). Prevalence of celiac disease in idiopathic short stature children presenting in OPD of children hospital, Faisalabad. *Annals of Punjab Medical College, 14*(1), 9-12. [DOI:10.29054/apmc/2020.706]

Mavroudi, A., Xinias, I., Papastavrou, T., Karatza, E., Fotoulaki, M., & Panteliadis, C., et al. (2007). Increased prevalence

of silent celiac disease among Greek epileptic children. *Pediatric Neurology, 36*(3), 165-169. [DOI:10.1016/j.pediatrneurol.2006.11.011] [PMID]

Rostami Nejad, M., Rostami, K., Emami, M., Zali, M., & Malekzadeh, R. (2011). Epidemiology of celiac disease in iran: A review. *Middle East Journal of Digestive Diseases, 3*(1), 5-12. [PMID] [PMCID]

Rozenberg, O., Rinawi, F., Haritan, Y., Yerushalmi, B., Kori, M., & Morgenstern, S., et al. (2020). Automated analyzers are suited for diagnosing celiac disease without a biopsy. *Journal of Pediatric Gastroenterology and Nutrition, 71*(1), 64-70. [PMID]

Rubio-Tapia, A., Hill, I. D., Kelly, C. P., Calderwood, A. H., Murray, J. A., & American College of Gastroenterology. (2013). ACG clinical guidelines: Diagnosis and management of celiac disease. The American Journal of Gastroenterology, 108(5), 656–677. [DOI:10.1038/ajg.2013.79] [PMID] [PMCID]

Schyum, A. C., & Rumessen, J. J. (2013). Serological testing for celiac disease in adults. *United European Gastroenterology Journal, 1*(5), 319–325. [PMID] [PMCID]

Sobhani Shahmirzadi, M., & Sohrabi, A. (2020). Comparison of tissue transglutaminase and anti-endomysial antibody tests in diagnosis of celiac disease. *Journal of Comprehensive Pediatrics, 11*(1), e87290. [DOI:10.5812/compreped.87290]

Taraghikhah, N., Ashtari, S., Asri, N., Shahbazkhani, B., Al-Dulaimi, D., & Rostami-Nejad, M., et al. (2020). An updated overview of spectrum of gluten-related disorders: Clinical and diagnostic aspects. *BMC Gastroenterology, 20*(1), 258. [DOI:10.1186/s12876-020-01390-0] [PMID] [PMCID]

Vieira, C., Jatobá, I., Matos, M., Diniz-Santos, D., & Silva, L. R. (2013). Prevalence of celiac disease in children with epilepsy. *Arquivos de Gastroenterologia, 50*(4), 290-296. [DOI:10.1590/S0004-28032013000400010] [PMID]

Xia, Y., Wu, Q., Wang, H., Zhang, S., Jiang, Y., & Gong, T., et al. (2020). Global, regional and national burden of gout, 1990-2017: A systematic analysis of the Global Burden of Disease Study. *Rheumatology, 59*(7), 1529-1538. [DOI:10.1093/rheumatology/kez476] [PMID]