Immune-Mediated Association Between Celiac Disease and Sensorineural Hearing Loss: A Systematic Narrative Review

Pietro De Luca[1], Alfonso Scarpa[1], Massimo Ralli[2], Domenico Tassone[3], Claudia Cassandro[4], Matteo Simone[3], Luca de Campora[3], Angelo Camaioni[3]

[1]Department of Medicine, Surgery and Dentistry, University of Salerno, Salerno, Italy
[2]Department of Sense Organs, Sapienza University, Rome, Italy
[3]Division of Otolaryngology, San Giovanni Addolorata Hospital, Rome, Italy
[4]Department of Surgical Sciences, University of Turin, Turin, Italy

Cite this article as: De Luca P, Scarpa A, Ralli M, et al. Immune-mediated association between celiac disease and sensorineural hearing loss: A systematic narrative review. *Turk J Gastroenterol.* 2022;33(4):273-279.

ABSTRACT

The auto-immune correlation between sensorineural hearing loss and celiac disease has previously been hypothesized. This review describes available evidence and offers insights for future perspectives. We searched the PubMed database. Studies in the review included children and adults with celiac disease evaluated for hearing loss. Individual case reports and review articles were excluded. The various searches turned in 32 results, of which 10 met the inclusion criteria. Auto-immune hearing loss has been proposed as extra-intestinal symptoms of celiac disease, despite the pathogenetic mechanisms being not entirely clear. Several studies postulated that subclinical hearing loss may be present in children with celiac disease. Despite existing literature not clarifying the link between celiac disease and sensorineural hearing loss, some authors proposed hearing screening in younger patients with celiac disease, to prevent the behavioral, cognitive, and sensorimotor impairment of hearing loss. Further rigorous studies are strongly recommended to better explore the relationship between hearing loss and celiac disease.

Keywords: *Anti-transglutaminase, celiac disease, gluten-free diet, immune-mediated disease, sensorineural hearing loss*

INTRODUCTION

Celiac disease (CD) is a chronic immune-mediated disorder triggered by gluten and related prolamines in genetically predisposed individuals. Celiac disease is the most frequent genetically based food intolerance and is characterized by the presence of a variable combination of gluten-dependent clinical manifestation, CD-specific antibodies, Human Leukocyte Antingens-DQ2 (HLA-DQ2) or Human Leukocyte Antingens-DQ2 (HLA-DQ8) haplotypes, and enteropathy.[1] The prevalence of CD is estimated to be more than 1% in the Western population, though the true prevalence of CD is difficult to establish owing to differences in clinical presentation. Diarrhea and other gastrointestinal symptoms can be observed in the early phase of CD, but they are not so frequent as in the past. Many patients (>50%)[2] exhibit several extra-intestinal manifestations, including neurological disorders such as headache, peripheral neuropathy, and epilepsy,[3,4] that can be present at the onset of the disease or become evident during its course. The etiopathogenesis of neurological complications are not yet entirely clear, and malabsorption alone does not explain the pathophysiology.

Sensorineural hearing loss (SNHL) is a type of hearing loss caused by damage of the inner ear or of the vestibulocochlear nerve (cranial nerve VIII). Immune-mediated SNHL has been widely reported[7] and has been described as a rare clinical entity characterized by progressive bilateral and asymmetrical SNHL.[5-7] The neurological correlation between SNHL and CD has previously been hypothesized since an immune-mediated mechanism can be the explanation both for CD and for CD-related neurological complications.[8]

The present paper aims to review the existing literature about the association between SNHL and CD and to discuss the possible mechanisms of this association.

MATERIALS AND METHODS

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist and statements recommendations.

Corresponding author: ***Pietro De Luca****, e-mail:* ***dr.dlp@hotmail.it***
Received: ***July 13, 2021*** *Accepted:* ***August 18, 2021*** *Available Online Date:* ***April 11, 2022***

DOI: ***10.5152/tjg.2022.21554***

Search Strategy

A comprehensive search strategy, developed in partnership with a medical librarian, was applied in PubMed, Cochrane, and Google Scholar databases, without time restriction applied in February 2021. Search items used include the following keywords: "celiac disease," "sensorineural hearing loss," "hearing loss," "coeliac disease." The search strategy was created in conjunction with these medical librarians using Medical Subject Headings intended for PubMed and then tailored for the other databases. Two independent investigators reviewed the resulting literature written in the English language. Duplicates articles were removed. Any disagreements regarding inclusion were resolved with a discussion between the 2 reviewers, and consensus was obtained. The PRISMA guidelines were followed in reporting the steps for inclusion of studies in this narrative review, and the full list of references was screened for potentially relevant articles.

Study Selection Criteria

The following were used as inclusion criteria for this study: subjects of all ages, with a diagnosis of CD according to the latest international guidelines, English language, more than 1 human subject, newly diagnosed CD patients or those on a gluten-free diet, and full-test availability. Animal studies, case reports, review articles, and commentaries were excluded. The articles were reviewed in full to assess the study objectives and level of evidence. The nature of this review did not require the Approval of the Local Ethic Committee.

Data Extraction

The reviewed articles were read in full by 2 of the authors, and each extracted data using a spreadsheet form. The data form included author(s), year of publication, country, number of subjects with CD, patient characteristics, type of study, auditory results, presence or absence of the comparison group, and size of the comparison group.

Main Points

- *Celiac disease (CD) is the most frequent genetically based food intolerance, and its prevalence is estimated to be more than 1% in the Western population.*
- *The neurological correlation between sensorineural hearing loss (SNHL) and CD has previously been hypothesized since an immune-mediated mechanism can be the explanation both for CD and for CD-related neurological complications.*
- *Several studies hypothesized that subclinical hearing loss may be present in young patients with CD and, according to this evidence, it could be predictive of more serious hearing, cognitive, and behavioral impairment at an older age.*

RESULTS

Study Selection

Through PubMed, Cochrane, and Goggle Scholar databases, we identified 64 records (Figure 1). After removal of duplicates, we screened 32 records and 21 were excluded since the object was obviously different. For eligibility, we assessed 11 full-test articles for inclusion/exclusion criteria. One article in Polish was excluded. Ten studies were included in the narrative synthesis, in which adult and pediatric patients with CD were evaluated for hearing loss. These studies were published over a period of 10 years, between 2007 and 2019.

Study Characteristics

Two studies were conducted in Italy, and eight studies were conducted in Turkey. Two studies were observational and eight were prospective.

Eight studies were conducted in newly diagnosed CD patients, and two studies both in newly diagnosed CD patients and patients on a gluten-free diet (GFD). A total of 573 patients (64% female) were evaluated. Two studies were conducted on adult patients, 7 on children, and 1 both in adults and children. The mean of ages across the studies ranged from 1 to 63 years. Several methods were used for the diagnosis of SNHL in patients with CD in the 10 selected studies. All patients were evaluated by pure tone audiometry to confirm hearing loss. Furthermore, speech audiometry to assess auditory impairment was reported in 3 studies, tympanometry in 8 studies, otoacoustic emissions (OAEs) in 2 studies, and auditory brainstem response (ABR) in 1 study. Across all studies, 573 patients were compared to 414 controls.

Individual Study Results

Search results are reported in Table 1. Leggio et al[8] reported that 10 (47.1%) CD patients and 2 (9.1%) healthy controls showed SNHL, with significantly higher prevalence of SNHL in the CD patients than in healthy control (P = .01) and no difference between untreated and treated CD patients. A mild bilateral SNHL (40%) and high-frequency SNHL (70%) were the most observed subtypes of hearing loss. A mild high-frequency SNHL in 5 (8.5%) CD patients and in 2 healthy controls (3.4%) were found by Volta et al[9] but the difference was not statistically significant (P = .219) and the prevalence of SNHL did not significantly differ

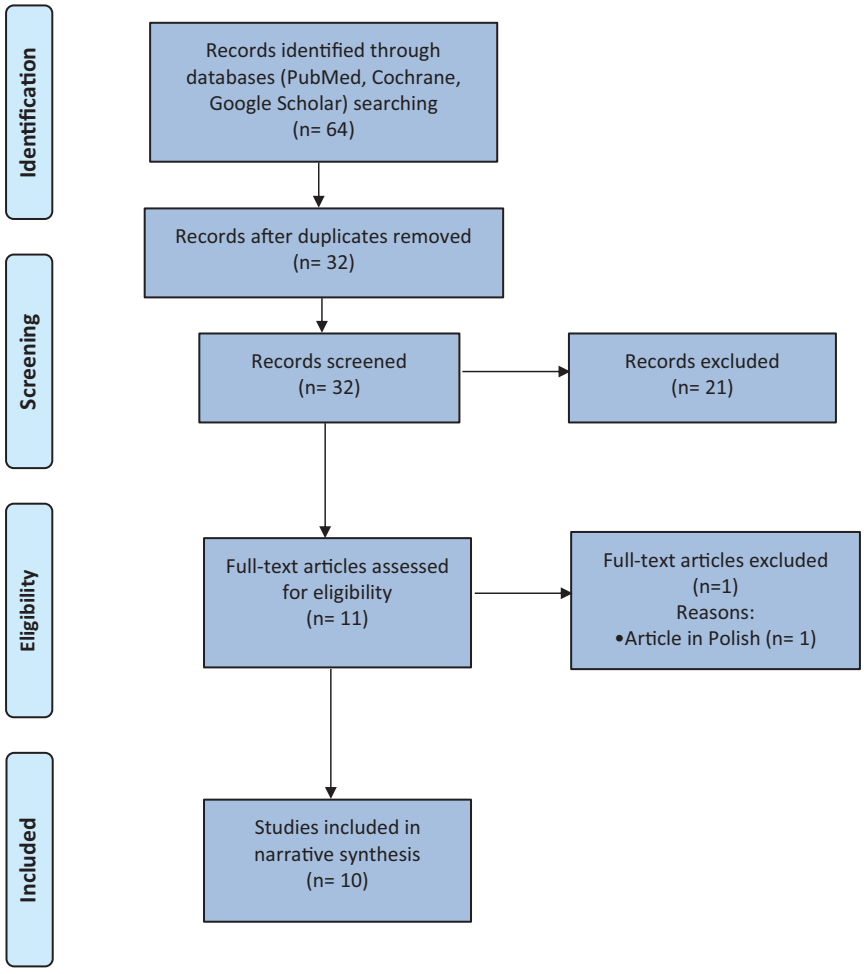

Figure 1. Trend changes of liver cancer mortality rate in the 6 WHO regions. WHO, World Health Organization.

between untreated and treated patients. On the contrary, in a study by Hizli et al[10] there was a higher frequency of SNHL in the CD group than in healthy controls (40.6% vs 3.1%, $P \leq .0001$) and slight/mild SNHL was the most common presentation of hearing loss. Karabulut et al[11] found a significant difference between the pure-tone threshold of the CD and the control group at 250 Hz ($P = .005$), and according to the pure-tone audiometry, the number of patients with SNHL was significantly higher in the CD group than in healthy controls ($P = .001$) and the signal to noise ratio (SNR) amplitudes in distortion product otoacoustic emissions (DPOAE) testing and the SNR amplitudes with and without contralateral acoustic stimulus in TEOAE testing were significantly lower at 1000 Hz in the CD compared to the control group. Solmaz et al[12] reported that there was no air-bone gap in any of the participants, speech discrimination was lower in the CD group ($P \leq .05$), and there was a significant difference of right and left ear pure tone threshold of CD patients and healthy controls ($P \leq .05$). On the contrary, Bukulmez et al[13] observed similar hearing functions of children with newly diagnosed CD and healthy controls. Other studies from Urgnaci et al[14] Sahin et al[15] Yazici et al[16] and Yaprak et al[17] did not show significant SNHL in overall measurements of patients with CD compared with controls and hypothesized that subclinical SNHL should be investigated in CD patients for recognizing hearing loss early during the course of the disease.

DISCUSSION

In 1958, Lehnhardt[18] described an "antigen-antibody reaction" in a cohort of 13 patients. The immune-mediated nature of a specific subtype of bilateral, often fluctuating, SNHL has been postulated in 1979 by McCabe[5]; he called it autoimmune inner ear disease (AIED), in which both cochlear and vestibular function of the inner ear was

Table 1. Characteristics of the Studies Included in the Present Review

Author, Country, Year	CD Group Sample Size	Comparison Group Sample Size	CD Group Mean Age (Range), year	CD Group Gender (M/F)	Study Design	Diagnosis of CD	Hearing Assessment	Hearing Results
Leggio, Italy, 2007	24	24	37.9 ± 11.4 (23-63)	2/22	Observational study in newly diagnosed CD adults and in those who had been on a GFD for at least 1 year	Positivity of antigliadin (AGA), Antiendomysium (EmA) and/or anti-tissue transglutaminase (anti t-TG) antibodies confirmed by the histological evidence of subtotal or total duodenal villous atrophy and increased intraepithelial lymphocytes and crypt hyperplasia	Pure tone audiometry Speech audiometry Timpanometry	The prevalence of HL was significantly higher in the CD patients than in the healthy controls (P = .01) and it was not significantly different between untreated (2/6; 33.3%) and treated (8/18; 44.4%) CD patients
Volta, Italy, 2009	59	59	34 (14-49)	9/50	Observational study in newly diagnosed CD children and adults and in those who had been on a GFD	CD biopsy proven	Pure tone audiometry	The prevalence of SNHL was not significantly different between CD patients and controls
Hizli, Turkey, 2011	32	32	11.9 ± 2.5 (7-15)	9/23	Prospective study in newly diagnosed CD children	Serology and biopsy-proven CD	Pure tone audiometry Timpanometry Speech audiometry	Higher prevalence of sensorineural hearing loss in CD group. Speech discrimination was also lower in CD than control group
Karabulut, Turkey, 2011	41	31	10.5 ± 3.9 (3-16)	12/29	Prospective study in newly diagnosed CD children	DNA	Pure tone audiometry Timpanometry TEOAE DPOAE Controlateral suppression of TEOAE	The threshold at 250 Hz of the patients with CD was significantly higher (P < .05 in CD compared to control group, P < .0001)
Solmaz, Turkey, 2012	25	25	10.82 ± 2.989 (6-17)	17/8	Prospective study in newly diagnosed CD children	Duodenal histology as a result of a villous atrophy (lesion type 3b–3c according to the Marsh-Oberhüber classification)	Pure tone audiometry Timpanometry	There was a statistically significant difference between the audiometric results in the CD and control groups (right ear and left ear) (P < .05)

(Continued)

Table 1. Characteristics of the Studies Included in the Present Review (Continued)

Author, Country, Year	CD Group Sample Size	Comparison Group Sample Size	CD Group Mean Age (Range), year	CD Group Gender (M/F)	Study Design	Diagnosis of CD	Hearing Assessment	Hearing Results
Bukulmez, Turkey, 2013	97	85	9.56 ± 4.37 (1.5-17)	41/57	Prospective study in newly diagnosed CD children	CD according to ESPGHAN criteria	Pure-tone audiometry Speech Audiometry Timpanometry Otoacustic emissions	No significant difference was found in celiac patients according to the Marsh–Oberhuber classification ($P > .05$)
Urganci, Turkey, 2014	44	20	8.8 ± 4.54 (1-16)	17/27	Prospective study in newly diagnosed CD children	CD according to ESPGHAN criteria	Pure tone audiometry Timpanometry	Pure tone audiometry did not show significant sensorineural hearing loss over all frequencies in patients with CD compared with controls ($P > .05$)
Sahin, Turkey, 2015	110	41	11.3 ± 3.1	41/69	Prospective study in newly diagnosed CD children	According to the ESPGHAN criteria with biopsy specimens analyzed according to the Marsh– Oberhuber classification	Pure-tone audiometry Timpanometry	Subclinical hearing loss may be present in children with CD
Yazici, Turkey, 2019	103	79	76 ± 13	44/59	Prospective study in newly diagnosed CD adults. CD patients were divided into two groups as remission or active, according to their gluten-free diet duration and serum levels of anti-t-TG	Positivity of anti-tissue transglutaminase (anti t-TG) antibody along with a tissue biopsy that showed histological evidence of subtotal or total duodenal villous atrophy, increased intraepithelial lymphocytes, and crypt hyperplasia as defined by the Marsh criteria and modified by Oberhuber	Pure-tone audiometry Timpanometry	There was no statistically significant difference between hearing levels of the CD patients and the control group in both measurements of air and bone conductions
Yaprak, Turkey, 2020	38	18	9.87 ± 4.326 (2-16)	15/23	Prospective study in newly diagnosed CD children	Duodenal biopsies and transglutaminase antibody (TGA) positivity	Pure tone audiometry Auditory brainstem response	No significant intergroup differences regarding hearing values

DNA, data not available; CD, celiac diseasae; GFD, gluten-free diet; HL, hearing loss; TEOAE, transient evoked otoacoustic emissions; DPOAE, distortion product otoacoustic emissions; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition.

damaged by an immunological process. Vestibular symptoms, such as imbalance, ataxia, and vertigo, may accompany the hearing loss in 50% of AIED patients.[19] Several autoimmune diseases, such as systemic lupus erythematosus, sarcoidosis, Hashimoto thyroiditis, and many others, are associated with AIED. Autoimmune inner ear disease is one of the few forms of SNHL that can potentially be treated; in the absence of specific diagnostic markers and uniformly accepted diagnostic criteria, AIED is defined by exclusion of other causes of SNHL and a positive response to corticosteroids.

The pathophysiology of AIED is not entirely clear, and several mechanisms, such as autoantibody development and deposition of immune complexes, have been proposed. Harris and Sharp[20] firstly demonstrated the presence of antibody directed against inner ear antigen latter (heat shock protein, HSP70). The possible neurological association between autoimmune SNHL and CD was first reported by Leggio et al[8] who reported a greater incidence of hearing loss in adult patients with CD; in this study, there were no differences between the prevalence of SNHL in untreated CD patients and in those in GFD, speculating that hearing loss in these patients could be permanent.

Another mechanism proposed is the vascular injury and consequent brain damage due to the low iron blood concentration observed in several patients with CD. Acute ischemic stroke and transient ischemic attacks can be secondary to iron deficiency anemia; similarly, the cochlear system could be interested by regional hypoperfusion due to damage of the labyrinthine artery.[21] Demyelination of cochlear nerve has also been proposed for SNHL in CD patients; Kao et al[22] suggested that mutations of osteoprotegerin (OPG), a regulator of bone remodeling and axonal myelination, could be responsible for hearing loss in several diseases, as Paget's disease or celiac disease. Osteoprotegerin deficiency/loss causes demyelination and degeneration of the cochlear nerve, activates ERK (extracellular signal-regulated kinase), and inhibits the surgical of cochlear stem cells, suggesting a mechanism for SNHL.[22] Another theory was offered by Garcia-Quintanilla and Miranzo-Navarro[23]; they proposed that the interaction of gliadin peptide on the human GRINA protein (a regulator of glutamate receptor ion channels) as the mechanism for hearing loss and other extra-digestive disorders of CD. Mice lacking the WPB2 (WW domain-binding protein 2) or GRID1 (glutamate inotropic receptor delta type subunit 1) gene showed hearing loss, suggesting that the inhibition of these regulating proteins by the 33-mer (the most immunodominant gluten peptide) could be responsible for hearing loss in humans.[24]

Clinical Implications and Future Research

This review highlights the importance of hearing consideration in pediatric and adult patients with CD; several studies hypothesized that subclinical hearing loss may be present in young patients with CD and, according to this evidence, it could be predictive of more serious hearing impairment at an older age. Further studies with longer follow-up will be required to expand the number of patients screened and eventually to reach a unanimous consensus. Furthermore, studies could evaluate the possibility that newly diagnosed CD patients and those on GFD should be evaluated separately to establish if GFD could improve possible hearing loss.

CONCLUSION

Auto-immune hearing loss has been proposed as extra-intestinal symptoms of CD, despite the pathogenetic mechanisms being not entirely clear. Several studies postulated that subclinical SNHL may be present in children with CD, and this could encourage hearing screening in younger patients with CD, in order to prevent the behavioral, cognitive, and sensorimotor impairment of hearing loss. Further rigorous studies with longer follow-up are strongly recommended to confirm this association and to establish proper treatments.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – P.D.L.; Design – P.D.L., A.S., M.R.; Supervision – A.C.; Resources – M.S., C.C., D.T.; Materials – L.D.C.; Data Collection – P.D.L., C.C., M.R.; Analysis and Interpretation – P.D.L.; Literature Search – A.S., C.C.; Writing Manuscript – P.D.L., M.R.; Critical Review – L.D.C., A.C.

Declaration of Interest: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012;54(1):136-160. [CrossRef]

2. Castillo NE, Theethira TG, Leffler DA. The present and the future in the diagnosis and management of celiac disease. Gastroenterol Rep. 2015;3(1):3-11. [CrossRef]

3. Gobbi G, Bouquet F, Greco L, et al. Coeliac disease, epilepsy, and cerebral calcifications: the Italian Working Group on Coeliac Disease and Epilepsy. Lancet. 1992;340:43943.
4. Cicarelli G, Della Rocca G, Amboni M, et al. Clinical and neurological abnormalities in adult celiac disease. Neurol Sci. 2003;24(5):311-317. [CrossRef]
5. McCabe BF. Autoimmune sensorineural hearing loss. Ann Otol Rhinol Laryngol. 1979;88(5 Pt 1):585-589. [CrossRef]
6. Ryan AF, Keithley EM, Harris JP. Autoimmune inner ear disorders. Curr Opin Neurol. 2001;14(1):35-40. [CrossRef]
7. Boulassel MR, Deggouj N, Tomasi JP, Gersdorff M. Inner ear autoantibodies and their targets in patients with autoimmune inner ear diseases. Acta Otolaryngol. 2001;121(1):28-34. [CrossRef]
8. Leggio L, Cadoni G, D'Angelo C, et al. Coeliac disease and hearing loss: preliminary data on a new possible association. Scand J Gastroenterol. 2007;42(10):1209-1213. [CrossRef]
9. Volta U, Ferri GG, De Giorgio R, et al. Sensorineural hearing loss and celiac disease: a coincidental finding. Can J Gastroenterol. 2009;23(8):531-535. [CrossRef].
10. Hizli S, Karabulut H, Ozdemir O, et al. Sensorineural hearing loss in pediatric celiac patients. Int J Pediatr Otorhinolaryngol. 2011;75(1):65-68. [CrossRef]
11. Karabulut H, Hizli S, Dagli M, et al. Audiological findings in celiac disease. ORL J Otorhinolaryngol Relat Spec. 2011;73(2):82-87. [CrossRef]
12. Solmaz F, Unal F, Apuhan T. Celiac disease and sensorineural hearing loss in children. Acta Otolaryngol. 2012;132(2):146-151. [CrossRef]
13. Bükülmez A, Dalgiç B, Gündüz B, Sari S, Bayazit YA, Kemaloğlu YK. The evaluation of hearing loss in children with celiac disease. Int J Pediatr Otorhinolaryngol. 2013;77(2):175-179. [CrossRef]
14. Urganci N, Kalyoncu D, Calis AB. Sensorineural hearing loss in pediatric patients with celiac disease. Eur Arch Otorhinolaryngol. 2015;272(9):2149-2151. [CrossRef]
15. Şahin Y, Durucu C, Şahin DA. Evaluation of hearing loss in pediatric celiac patients. Int J Pediatr Otorhinolaryngol. 2015;79(3):378-381. [CrossRef]
16. Yazıcı A, Yıldırım AE, Konduk BT. Does celiac disease cause autoimmune sensorineural hearing loss? Turk J Gastroenterol. 2019;30(9):776-781. [CrossRef]
17. Yaprak N, Sayar E, Derin AT, Bostancı A, Turhan M, Yılmaz A. Hearing evaluation with ABR in pediatric patients with celiac disease. Turk J Gastroenterol. 2020;31(2):163-166. [CrossRef]
18. Lehnhardt E. Sudden hearing disorders occurring simultaneously or successively on both sides. Z Laryngol Rhinol Otol. 1958;37(1):1-16.
19. Ciorba A, Corazzi V, Bianchini C, et al. Autoimmune inner ear disease (AIED): a diagnostic challenge. Int J Immunopathol Pharmacol. 2018;32:2058738418808680. [CrossRef]
20. Harris JP, Sharp PA. Inner ear autoantibodies in patients with rapidly progressive sensorineural hearing loss. Laryngoscope. 1990;100(5):516-524. [CrossRef]
21. Lemajic-Komazec S, Abenavoli L. Celiac disease and hearing loss. Bratisl Lek Listy. 2017;118(9):570. [CrossRef]
22. Kao SY, Kempfle JS, Jensen JB, et al. Loss of osteoprotegerin expression in the inner ear causes degeneration of the cochlear nerve and sensorineural hearing loss. Neurobiol Dis. 2013;56:25-33. [CrossRef]
23. Garcia-Quintanilla A, Miranzo-Navarro D. Extraintestinal manifestations of celiac disease: 33-mer gliadin binding to glutamate receptor GRINA as a new explanation. BioEssays. 2016;38(5):427-439. [CrossRef]
24. White JK, Gerdin AK, Karp NA, et al. Genome-wide generation and systematic phenotyping of knockout mice reveals new roles for many genes. Cell. 2013;154(2):452-464. [CrossRef]