Does celiac disease cause autoimmune sensorineural hearing loss?

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ABSTRACT

Background/Aims: *The primary aim of this study is to identify whether an autoimmune sensorineural hearing loss is an extraintestinal neurological manifestation in adult CD patients. The secondary aim is to identify whether the duration of a gluten-free diet has an effect on the hearing levels of CD patients.*

Materials and Methods: *This prospective study consisting of 103 adult CD patients and 79 healthy controls between May 2012 and August 2018 at the University of Gaziantep Gastroenterology and Otorhinolaryngology Departments. 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. The control group was checked both for CD symptoms and anti-t-TG serum levels. Both participants performed a pure tone audiometry after detailed ear nose and throat examination.*

Results: *Only 4 of 103 CD patients showed sensorineural hearing loss. 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. The hearing levels comparing the remission and active CD patients did not show any difference in air and bone conduction frequencies.*

Conclusion: *In this study with a higher number of CD patients when compared with the previous studies, it has been shown that CD does not appear to cause autoimmune sensorineural hearing loss. In addition, the status of the patients regarding the activeness or the remission of CD did not display a differ between the CD patients in terms of hearing levels.*

Keywords: *Celiac disease, autoimmune, sensorineural hearing loss*

INTRODUCTION

Celiac disease (CD) is defined as an immune-mediated small intestinal inflammatory disease that is characterized by malabsorption due to intestinal inflammation, which leads to villous atrophy followed by crypt hyperplasia. This inflammation results from a T-cell-driven auto-destructive process with the ingestion of gluten-containing cereals such as wheat, rye, barley, and oat. The CD patients are in close genetic association with the human leukocyte antigen HLA DR3/DQ2 (mainly DQA1*0501-DQB1*0201; 85-95%), HLA DR4/DQ8 (DQA1*0301-DQB1*0302; 5-15%), or both haplotypes (1-3).

Celiac disease is a disorder that can cause autoimmune sensorineural hearing loss (SNHL), which is thought to share the same pathophysiologic mechanism as other autoimmune disorders. (4,5) The pathology of autoimmune hearing loss might be related to different mechanisms such as autoreactive T-cells, immune complex depositions, or autoantibodies (5,6). Many of these autoimmune diseases, such as Behçet's Disease, systemic lupus erythematosus (SLE), and antiphospholipid antibody syndrome (APS) may cause hearing loss with thrombosis of labyrinthine vessels, which results in cochlear involvement (6,7). Patients with CD may be at an increased risk of developing venous thromboembolism (VTE) due to chronic inflammation and vitamin deficiency (8). A significantly increased risk of VTE among patients with CD was demonstrated in a recent meta-analysis (8).

Hearing loss is a common disorder in the general population and is divided into three distinct and broad groups, namely: SNHL, conductive-type hearing loss, and mixed-type hearing loss (9). SNHL represents the major hearing loss group, which consists of 90% of all cases (9). Age is the most discussed factor that plays an essential role in the prevalence of SNHL. In the literature, for individuals aged 12 years and older, the estimated SNHL rate was found to be 14.3% for both ears and 22.7% for a single ear yearly (10). Although the data about SNHL being an extraintestinal manifestation of CD is controversial, SNHL is extensively described in the

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literature. Despite the existence of studies that regard autoimmune SNHL as an extraintestinal manifestation of CD in children, there is no consensus on whether SNHL is an extraintestinal finding in adult patients with CD (9-14). The main purpose of this study is to investigate if there is any association of autoimmune SNHL with CD by recruiting a greater number of adult CD patients as compared to the previous reports.

MATERIALS AND METHODS

A total of 128 patients who were diagnosed with CD between May 2012 and August 2018 at the Gaziantep University otorhinology clinic were enrolled in this study to evaluate autoimmune hearing loss. The diagnosis of CD was based on the 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 (15). SNHL was defined by pure tone audiometry after otoscopic examinations, which were performed in a sound-proof room at the Otorhinology Clinic of Gaziantep University between February 2018 and August 2018. The patients who had perforated eardrums, absence of acoustic reflex, diabetes mellitus, neurologic, and metabolic disorders with a type of hearing loss, cardiovascular diseases, and chronic or acute otologic infectious diseases were excluded from the study. A total of 103 CD patients met the inclusion criteria and were enrolled in the study. Of these, 16 patients had been recently diagnosed with CD and had been on gluten-free diets (GFDs) for more than 6 months; they were all in remission.

All the CD patients were evaluated for the commonly encountered autoimmune diseases that could potentially cause SNHL. For SLE, the systemic lupus international collaborating clinics criteria were used, where four of the 17 criteria were required to be evaluated further. For Behçet's disease, the patients were checked for recurrent aphthous ulceration involving the oral mucosa and the genital area, for ocular involvement such as hypopyon, panuveitis, or retinal vasculitis, and for neurologic disease with characteristic central nervous system parenchymal findings. The existence of vascular diseases due to SLE, such as pulmonary artery aneurysms, Budd-Chiari syndrome, and cerebral venous thrombosis were also assessed. Detection of a positive pathergy test in any subject was accepted as an exclusion criterion for the study. If two simultaneously existing clinical scenarios were found, further investigation was planned for the diagnosis of the antiphospholipid syndrome and these patients were also excluded from the study. These conditions included the occurrence of one or more otherwise unexplained venous or arterial thrombotic events (especially in young patients) and/or one or more specific adverse outcomes related to pregnancy (which includes fetal death after the 10^{th} week of gestation, premature birth due to severe preeclampsia, placental insufficiency, or multiple embryonic losses (<10^{th} week of gestation). According to the assessment of the autoimmune conditions explained above, none of the CD patients in the present study had any clinical findings related to the conditions which might cause hearing loss.

Evaluation of bilateral middle ear pressure status was performed with the tympanometry test (GSI 33 Middle Ear Analyzer) in all participants. Only participants who displayed a Type A tympanogram reading were included in this study.

Assessment of hearing levels were accomplished by the pure tone audiometry test (Interacoustics AC 40 Clinical Audiometer, Denmark). Bone and air conduction thresholds at 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz were detected. Pure tone average was detected by taking the averages of 500 Hz, 1000 Hz, and 2000 Hz thresholds. According to the classification of hearing loss by the World Health Organization, the value of pure tone at an average of over 25 dB is accepted as hearing loss. In the same classification, pure tone levels between 25-40 dB are accepted as mild, 40-60 dB are moderate, 60-80 dB are severe, and over 80 dB are referred to as profound hearing loss.

The CD patients were divided into two groups: active and remission, according to their anti t-TG levels and duration of gluten-free diet. Of the 103 patients, 87 comprised the remission group; they had been on GFDs for more than 6 months and had an undetectable value of anti t-TG antibody (below 19 RU/mL). The remaining 16 patients comprised the non-remission CD group (active group); they had been on a GFD for less than 6 months, if at all, and had detectable levels of anti t-TG (over 19 RU/mL).

The control group was created with the same age- and gender-matched healthy subjects comprising hospital employees, physicians, and medical students using the same exclusion criteria. The entire control group was tested for serum anti t-TG antibody levels and only the individuals with negative test results were included in this research.

Statistical analysis

The Kolmogorov-Smirnov test was used to check the normal distribution of continuous variables. This was followed by an independent sample t-test, which was applied to find the statistical significance between both groups' hearing levels. The Statistical Package for Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA) software was used for statistical analysis and a p-value of under 0.005 was accepted as statistically significant.

Written consent was obtained from all participants enrolled in this study. The ethics committee of the Gaziantep University approved this study (approval number: 2018/69).

RESULTS

A total of 103 CD patients and 79 control patients were enrolled in this prospective study, where 59 patients were female (57, 14%) and 44 patients were male (42, 86%). The mean age of the study group was 28 years (76±13

Table 1. The comparison of hearing levels at different frequencies between celiac disease and control groups.

	Celiac Group (n=206 ear) Mean±Std Dev			Control Group (n=158 ear) Mean±Std Dev			
Frequency	Right	Left	Total	Right	Left	Total	p
Air500	8.11±5.5	7.82±4.7	8.35±5	8.67±4.4	9.37±4.1	9.01±4.3	0.459
Air1000	7.77±5.7	7.57±5	7.77±4.7	7.78±3.6	8.04±3.8	7.91±3.7	0.697
Air2000	7.86±5.8	8.3±6.7	8.08±6.2	6.96±3.2	8.29±4	7.62±3.7	0.991
Air4000	9.56±7	9.56±7.7	9.56±7.3	11.20±7.7	12.91±9.7	12.05±8.7	0.138
Air8000	13.74±10.7	13.93±11.6	13.73±11.1	16.46±11.6	16.33±11.6	16.39±11.5	0.104
Bone500	14.08±5.7	14.22±6.9	14.15±6.3	13.35±4.9	13.16±4.9	13.25±4.9	0.251
Bone1000	12.52±6.5	11.89±6.4	12.2±6.4	11.77±4.8	11.65±4.9	11.7±.8	0.391
Bone2000	12.09±6.9	12.38±8.1	12.23±7.5	10.95±4.2	11.77±5.4	11.36±4.8	0.203
Bone4000	14.61±8.2	14.56±9.3	14.58±8.7	15.44±8.5	17.22±10.3	14.2±9.5	0.072
Bone8000	17.77±11.2	17.96±12.7	17.86±11.9	20.82±12.1	20.89±12.1	20.85±12	0.081
PTA*of Bone	13.31±5.8	13.26±6.4	13.29±6.1	12.87±4.5	13.44±4.8	13.16±4.6	0.58
PTA*of Air	8.31±5.3	8.31±5.3	8.31±5.3	8.65±3.6	9.65±3.8	9.15±3.7	0.063

PTA*: Pure tone average.

Table 2. Comparison of hearing values at different frequencies of celiac patients in active and remission groups.

	Active Celiac N=16 Mean±Std Dev			Control Group (n=158 ear) Mean±Std Dev			
Frequency	Right	Left	Total	Right	Left	Total	p
Air500	8.43±4.2	8.43±4.2	8.43±4.2	8.04±5.6	7.61±4.8	7.87±5.2	0.57
Air1000	8.43±4.2	6.87±2.9	7.65±3.7	7.64±5.9	7.7±5.3	7.67±5.6	0.55
Air2000	7.5±3.9	6.87±2.9	7.18±3.5	7.93±6.1	8.56±7.1	8.24±6.6	0.359
Air4000	7.81±3.9	7.81±3.5	7.81±3.7	9.88±7.4	9.77±8.1	9.88±7.8	0.108
Air8000	17.5±3.9	14.06±9.3	15.78±7.4	13.85±11.4	13.7±11.9	13.87±11.6	0.633
Bone500	13.75±3.4	13.75±5.1	13.75±4.8	12.06±5.6	14.14±7.2	13.18±7.1	0.741
Bone1000	15±3.5	10.93±4.9	12.96±4.4	12.06±6.8	11.93±6.7	12.06±6.7	0.099
Bone2000	11.87±4.6	10±5.1	11.25±4.6	12.12±7.2	12.7±8.5	12.41±7.9	0.177
Bone4000	13.43±4.9	11.47±5.8	12.81±5.1	14.8±8.6	14.82±9.8	14.9±9.2	0.113
Bone8000	17.5±3.9	17.05±10.1	17.81±7.2	17.8±12	17.7±13.2	17.8±12.6	0.849
PTA*of Bone	13.51±3.4	11.17±4.5	12.69±3.6	13.29±6.2	13.36±6.9	13.4±6.5	0.179
PTA*of Air	8.04±3.6	7.77±2.9	7.05±3.3	8.37±5.6	8.46±5.6	8.41±5.6	0.334

PTA*: Pure tone average.

years), 49 years in the CD group, and 35 7±11, 29 years in the control group, respectively. There was no statistically significant difference between the CD and control group in terms of age or gender (p=0.37).

Only four of the 103 CD patients had hearing loss at the pure tone averages. The first CD patient was a 20-year-old male who showed moderate (42 dB) SNHL in the right ear and a normal hearing level in the left ear. Additionally, it was found that this patient had a normal hearing level according to pure tone audiometry (Left: 15 dB, Right: 17 dB), which was performed in the same clinic 4 years ago. The second CD patient was a 41-year-old female who had mild SNHL in both the left (28 dB) and the right ear (34 Db). The third CD patient was a 62-year-old male who showed moderate SNHL in both the left (44dB) and the right (53 dB) ear. The fourth CD patient was 61-year-old male who had mild SNHL in the right ear (32 dB) and normal hearing in the left ear (20 dB). No hearing loss was detected in the control group.

Anti t-TG levels were positive and high (over 200 RU/ mL) in the 20-year-old male CD patient who had displayed right SNHL. The remaining CD patients with SNHL demonstrated negative anti t-TG antibodies. Except for one of these four patients, all of them were on GFDs for more than 6 months and they all had undetectable levels of anti t-TG antibody before the hearing assessment was performed.

In the overall comparison of the hearing levels at 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz frequencies, both air and bone conduction did not show any statistically significant difference between the CD and control group, as shown in Table 1. Pure tone average hearing levels, both in the bone and air conduction levels, did not show any statistically significant difference in the CD and control groups.

Both the active and remission groups of CD were compared based on the hearing levels at 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz frequencies in both air and bone conduction; they did not show any statistically significant difference. Also, there was no statistical difference between these two groups in terms of pure tone average hearing levels, as shown in Table 2.

DISCUSSION

In several studies, there have been attempts to find a possible relationship between CD and SNHL (9-12,14). In some of these studies, it has been concluded that there is a relationship between SNHL and CD, and the main mechanism for this hearing loss was an autoimmune ear disorder (9,13). To identify any hearing loss as an autoimmune disorder, there has to be laboratory evidence of an immune response directed at the sensorial hearing mechanisms of the inner ear and thus, there should be a positive response to immunosuppressive treatment (6). In this study, the researchers did not find a significant correlation between SNHL and CD. However, only one male patient with SNHL had a normal hearing level according to a pure tone audiometry test that was performed 4 years ago. None of the etiologic factors for SNHL, such as noise exposure, trauma (including barotrauma), infectious ototoxic drugs, or tumors were found in our 20-year-old male CD patient. Further investigation and a close follow-up (2-3 pure tone audiometry tests per year) have been planned for this patient.

The overall incidence of severe or profound SNHL for patients over the age of 12 is declared at 2.5% in the general population; 22.7% of these patients presented with SNHL, at least unilaterally (10). The rates of hearing loss of the CD patients in this study were not different than that of the general population and two patients were over 60 years of age. The autoimmune SNHL as an extraintestinal neurologic component of CD was first described by Leggio et al. (9) in 10 of 24 CD patients. However, Volta et al. (11) showed that there were only 5 SNHL patients out of 48 CD patients, and only two of the five patients had positive antineuronal antibodies. According to researchers' data, there was no statistically significant positivity of anti-neural antibodies, which is regarded as a finding of an autoimmune ear disorder. The hearing level results from this study are represented by a greater number of CD patients and are compatible with the findings reported by Volta (11).

The neurologic autoimmune component of CD includes many diverse conditions, such as cerebellar ataxia, peripheral neuropathy, and epilepsy (16,17). According to previous reports, many of these neurologic conditions improves with the implementation of a GFD (18-20). Despite the presence of other neurologic situations, improvement in the hearing levels according to the GFD duration and/or the status of the active or remission CD remains scarce (13,21). The hearing impairment was found only at different frequencies for bone conduction in the non-GFD CD patients (GFD time: under 36 months) according to a report by Şahin et al. (13) However, another study with similar patients and control groups revealed that 17 of 44 CD patients were non-compliant with GFD and only one of these patients developed SNHL. Accord-

ing to the results of this study, the duration of GFD did not seem to affect the hearing levels of CD patients in remission (those who had negative anti-t TG levels that are not mentioned in the literature). Additionally, for the diagnosis of autoimmune hearing loss, the initial treatment should start with prednisone 1 mg/kg/day with a maximum dose of 60 mg/day for 4 weeks (22,23). None of the previous research claimed that autoimmune SNHL is an extraintestinal manifestation of CD, and did not comment on the improvement in hearing loss after prednisone or other immunosuppressant therapy.

One of the limitations of this study is the absence of evaluation of anti-neural antibodies in CD patients. The patients' relatively short follow-up period with hearing loss is another limitation, even though the SNHL patients were not started on empirical corticosteroid treatment. The beneficial effects of corticosteroid treatment are not free of significant side effects, which may be seen in relatively small doses, starting from >7.5 mg/day (24).

In conclusion, the hearing levels of CD patients do not seem to differ from that of the general population. Further, autoimmune SNHL is not considered as a neurologic finding that is induced by CD. Routine hearing level assessment for CD patients does not seem to be necessary, and this assessment should be reserved only for those CD patients who display clinical findings of hearing loss.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gaziantep University (Approval Number: 2018/69).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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