The Journal of International Advanced Otology

J Int Adv Otol 2020; 16(3): 362–6 • DOI: 10.5152/iao.2020.6035

Original Article

Assessment of Hearing Function in Children with Inflammatory Bowel Disease

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Cite this article as: Polat E, Çınar Z, Keskindemirci G, Yiğit Ö, Kutluk G, Türe M, et al. Assessment of Hearing Function in Children with Inflammatory Bowel Disease. J Int Adv Otol 2020; 16(3): 362-6.

OBJECTIVES: Inflammatory bowel disease (IBD), a chronic pathology that affects many organ systems, appears after dysregulated immune response in genetically predisposed patients. Inner organ involvement has been shown in various autoimmune diseases because of its immunosensitivity. In this study, we aimed at showing sensorineural hearing loss (SNHL) as a result of possible subclinical inflammation in patients with IBD during the remission period.

MATERIALS and METHODS: We included 32 children with IBD and 31 healthy volunteers with comparable sex and age. Detailed ear-nose-throat examination was conducted for all, and patients were excluded if they had a history of ear infectionor trauma. Thereafter, the results of pure tone audiometry (PTA), high-frequency audiometry, and distortion product otoacoustic emissions testing were compared between the groups.

RESULTS: There were no differences in terms of age, sex, and PTA values between controls and children with IBD. No statistical differences were found between responses at 250; 500; 2,000; 4,000; DP1000; DP1400; DP2000; DP2800;and DP4000 Hz as well as the signal-to-noise ratio (SNR) at 1,000 Hz when the controls and children with IBD ($p>0.05$ for all) were compared. However, the mean responses at 1,000; 8,000; 10,000; 12,500; 16,000; SNR1400; SNR2000; SNR2800; and SNR4000Hz of the children with IBD were significantly higher than those of the controls ($p<0.05$ for all).

CONCLUSION: Initial SNHL appears at high frequencies in pediatric patients with IBD.

KEYWORDS: Children, inflammatory bowel disease, cochlear functions, inflammation

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disease that is seen in genetically susceptible individuals and can affect many organ systems due to immune dysregulation [1]. Extraintestinal manifestations arise in 20% to 40% of patients with IBD, and theyoccur as a result of increased intestinal permeability causing systemic immune response by luminal antigens [2-4]. All the immune-sensitive organs can be the targets of this immune response. Inner ear involvement has been shown in various autoimmune illnesses because of its immunosensitivity [5-7]. Sensorineural hearing loss (SNHL) is the most frequent ear pathology in patients with IBD [8].

McCabe first recognized SNHL associated with immunity in 1979 [9]. He reported 18 patients whose SNHL was responsive to steroids and immunosuppressive therapy. Thereafter, immunity-related diseases, such as rheumatoid arthritis, Sjogren's syndrome, polyarteritis nodosa, Behcet's disease, and familial Mediterranean fever, have been associated with an increase in SNHL [10-12].

This study was presented at the 39. Turkish National Otorhinolaryngology Head and Neck Surgery Congress, 8-12 November 2017, Antalya, İstanbul.

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Submitted: 09.21.2018 • **Revision Received:** 03.31.2020 • **Accepted:** 04.09.2020
Available online at www.advancedotology.org

Mechanisms causing inner ear involvement were Tlymphocyte–associated cytotoxicity, vasculitis, and immune complex accumulation. Although the exact mechanism is still unknown, it is believed that cochlear damage occurs after type 4 or delayed type cellular hypersensitivity reaction as a result of antigen release, causing T cell sensitization in circulation [10]. Other proposed mechanisms include accumulation of immune complexes inducing complement fixation and type 3 hypersensitivity due to the release of chemotactic factors and vasoactive amines. Vasculitis, which appears in the subendothelial layer in small vessels, such as labyrinthine arteries, causes ischemia and damage to the organ of Corti [13].

Studies conducted on adults with IBD showed that SNHLcan be seen in 46%-57% cases as an extraintestinal manifestation [14-17]. There are various studies assessing hearing loss in patients with IBD, but almost all have included adult population [15, 16, 18-20]. Subclinical hearing loss in IBD is a novel topic in the pediatric otolaryngology literature. A study comparing children with IBD and controls revealed that pure tone audiometry (PTA) did not show significant SNHL over all frequencies from 250 to 8000 Hz [21]. For the pediatric age group with IBD, we were able to find just a few studies on the hearing functions. Moreover, 2 case studies presented 2 adolescents aged 15 and 16 years with acute SNHL, and anotherstudy included limited number of children, which was conducted by Kalyoncu et al. [21-23]. Because of data scarcity on this subject, we aimed at studying the hearing functions of pediatric patients who were diagnosed with IBD using both objective and subjective audiological tests. We aimed at assessing SNHL possibly due to subclinical inflammation in children with IBD during the remission period.

MATERIALS AND METHODS

Patients

Informed consent forms were filled by the parents of the children before enrollment. A total of 32 children (11 women and 21 men) with IBD who were followed up in the Department of Pediatric Gastroenterology in University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital, Department of Pediatric Gastroenterology between April 2017 and June 2017 were included in the study. Moreover, 31 age- and sex-matched healthy volunteers were included as controls. All patients were in theremission period. Patients' gender, age, age at diagnosis, pediatric ulcerative colitis activity index (PUCAI) or pediatric Crohn's disease (CD) activity index at diagnosis, area of involvement, presence of extraintestinal involvement, and treatment were recorded.

PUCAI has 6 different items (abdominal pain, rectal bleeding, stool consistency of most stools, number of stools per 24 hours, nocturnal bowel movement, and activity level) and is scored between 0 and 85[24]. A total score of <10 points and a change in score of at least 20 points indicates remission. Scores over 10 points represent mild, moderate, or severe disease activity [25].

The pediatric CDactivity index stratifies the severity of the disease in patients aged ≤19 years; has11 items; and combines essential subjective information, examination findings, and laboratory results into a single score [26]. The maximum possible score is 100, and each decrease in score by 12.5 points indicates clinically significant response to therapy [27].

Audiological Involvement

Patients who had previous ear infection, trauma,orany other associated illness were excluded, and their detailed ear-nose-throat (ENT) examination, PTA, high-frequency audiometry (HFA), and distortion product otoacoustic emission (DPOAE) test were conducted in the Department of ENT. The tests were conducted once. During the tests, all participants were kept in a soundproof room. Pure audio, air, and bone audiometry testresults were analyzed including high frequencies using AC40 Clinical Audiometer (AC40 Diagnostic Audiometer, Interacoustic Company, Assens, Denmark).

PTA was performed at frequencies of 250; 500; 1,000; 2,000; and 4,000 Hz, and HFA was performed atfrequencies of 8,000; 10,000; 12,500; and 16,000 Hz. In these frequencies, normal hearing threshold was accepted under 15dB (decibel). DPOAE test is accepted as a marker that shows early cochlear damage. DPOAE response characteristics were evaluated at 1,000; 1,400; 2,000; 2,800; and 4,000 Hz using Otodynamics (Otodynamics ILO-288 Echoport equipment, Otodynamics Ltd., Hatfield, UK). Additionally, the signal-to-noise ratio (SNR) was accepted as an indicator that reflects the reliability of DPOAE. The local ethics committee of Kanuni Sultan Suleyman Training and Research Hospital approved the study with the confirmation number of 1067.

Statistical Analysis

Statistical analyses were conducted using the Number Cruncher Statistical System 2007 statistical software (UT, USA) program. Besides the descriptive statistical methods (mean, standard deviation, median, and interquartile range), the Kolmogorov–Simirnov test was used to compare the groups that are normally distributed and the Mann–Whitney U test was used for the groups that were not normally distributed. To compare the qualitative data, the chi-square test was used. A $p<0.05$ was considered significant.

RESULTS

Demographic Data

There were no statistically significant differences in terms of mean age and sex between the patients with IBD and controls (Table 1). Furthermore, patient characteristics did not differ between children with UC and CD in the patient group (Table 2).

Audiological Data

Although no statistical differences were found between the mean values of response characteristics of PTAatfrequencies of 250; 500; 2,000; and 4,000 Hz between the patients with IBD and controls, the values were significantly higher at 1,000; 8,000; 10,000; 12,500;and

MAIN POINTS

- Hearing system involvement is not uncommon in patients with IBD.
- Assessment of Cochlear functions is guiding in assessing sensorineural hearing loss.
- A hearing test to be performed twice a year will be useful for early diagnosis.

Table 1. Demographic data of control and patient with inflammatory bowel disease groups

		Control group		Patient (with IBD) group			
		Mean±SD	Median	Mean±SD	Median	p	
Age		13.3±3.2	15.0	14.2±3.8	15.5	0.092	m
Gender	Female	18	58.1%	11	34.4%	0.059	X^2
	Male	13	41.9%	21	65.6%		

IBD: inflammatory bowel disease; SD: standard deviation

Table 2. Characteristics of the children with Crohn's disease or ulcerative colitis in the patient group

Characteristic	Children with ulcerative colitis (n=15)	Children with Crohn's disease (n=18)	p*
Male	71.4%	61.1%	0.712
Mean age, years	13.7±3.7	14.4±3.8	0.528
Mean age at diagnosis	12.0±4.0	11.9±4.3	0.905
Mean age at the beginning of complaints	10.9±3.8	11.3±4.7	0.738
Duration of illness (months)	42.2±29.3	38.3±27.0	0.846
Duration of treatment (months)	35.4±29.2	28.7±20.4	0.723
Mean activation index at diagnosis	1.6±1	2.3±0.6	0.067
Perianal involvement	30%	33%	1.0
Extraintestinal involvement	20%	40%	0.402

*Mann–Whitney U test and χ2test where available

16,000 Hz in the patient group. No statistically significant differences were seen in the response characteristics of DPOAE at 1,000; 1,400; 2,000; 2,800; and 4,000 Hz frequencies. Although no significant difference was observed inthe response values of SNR at 1,000 Hz between the 2 groups, the values differed statistically at SNR1400, SNR2000, and SNR4000 Hz (Table 3).

When patients with CD and UC were compared, no difference was observed for age; sex; PTA; hearing responses from 250 to 16,000 Hz; DPOAE responses from 1,000 to 4,000 Hz; and SNR responses from 1,000 to 5,000 Hz. The activation index was significantly different between the time of diagnosis and audiological tests, and it was low when the tests were conducted. The diseases were under control at the study time (data were not shown).

DISCUSSION

It was postulated that genetic and environmental factors and the interference between the intestinal microbiota and mucosal immunity play roles in the etiology of IBD. Well-defined extraintestinal manifestations of IBD include uveitis, iritis, erythema nodosum, pyoderma gangrenosum, primary sclerosing cholangitis, ankylosing spondylitis, and prothrombotic predisposition [14]. The occurrence risks of other autoimmune diseases havealso increased because of immune dysregulation. Inner ear involvement has been shown in various autoimmune diseases, such as systemic lupus erythematosus, Kawasaki disease, Wegener granulomatosis, and rheumatoid arthritis [15].

Table 3. PTA, high-frequency thresholds, DPOAE, and SNR values of controls and patients (with IBD)

	Control group	Patient group	p
PTA	8.7±3.7	7.5±4.5	0.166
250 HZ	13.3±6.1	10.8±5.2	0.076
500 HZ	10.6±4.7	8.9±4.4	0.171
1000 HZ	8.9±3.0	6.4±5.4	0.004
2000 HZ	7.2±5.2	5.0±4.2	0.080
4000 HZ	7.0±6.4	7.0±5.1	0.740
8000 HZ	8.8±7.3	14.1±8.5	0.006
10,000 HZ	5.3±5.8	24.8±11.1	<0.0001
12,500 HZ	6.1±5.8	23.8±11.9	<0.0001
16,000 HZ	5.3±5.3	29.5±16.5	<0.0001
DP1000 HZ	6.2±7.4	5.7±7.6	0.657
DP1400 HZ	8.9±8.7	9.8±8.8	36
DP2000 HZ	8.5±8.213		
DP2800 HZ	3.3±9.8	6.7±9.4	0.118
DP4000 HZ	7.1±7.6	7.8±8.4	0.811
SNR1000 HZ	5.6±9.8	8.6±7.6	0.314
SNR1400 HZ	11.3±9.5	15.3±9.6	0.034
SNR2000 HZ	10.7±10.6	16.7±9.4	0.009
SNR2800 HZ	9.0±10.3	16.5±9.4	0.001

PTA: pure tone audiometry; IBD: inflammatory bowel disease; DPOAE: distortion product otoacoustic emissions; SNR: signal-to-noise ratio.

Casella et al. [28] found that the rate of SNHL was <2% in adults suffering from IBD. Akbayir et al. [15] introduced subclinical SNHL over high frequencies (2, 4, and 8 kHz) in adults with UC or CD compared withthe controls. They emphasized that the most evident decrease was seen at 4 kHz for adults with CD, whereas it was at 2,4, and 8 kHz for adults with UC compared with that forthe controls. To assess the audiovestibular involvement, the authors conducted PTA test at 0.5, 1, 2, 4, and 8 kHz frequencies.

In diseases that course with systemic inflammation and vasculitis, such as primary Sjögren's disease, Behcet's disease, and systemic lupus erythematosus, it was proved that SNHL was over higher frequencies (from 8,000 to 16,000 Hz) rather than the lower ones [12, 29-31]. In this study, we assessed hearing loss with detailed PTA including higher frequencies up to 16,000 Hz (9 consecutive frequencies from 250 to 16,000 Hz) in pediatric patients with IBD. Compatible with

the results of the study conducted by Kalyoncu et al. [21], we could not find statistically significant difference for the mean values of PTA tests between the patients with IBD and controls. However, differently, we found that our patients with IBD had significantly higher values higher PTA values at 1,000 and 8,000 Hz than the controls. Another distinctive feature of our study from the studies conducted on adults with IBD or from the study by Kalyoncu et al. [21], is that we examined detailed HFA tests including 10,000 through 16,000 Hz. Thus, we were able to find that children with IBD had statistically significant SNHL over higher frequencies (10,000; 12,500; and16,000 Hz). This finding suggests that in patients with IBD, SNHL initially appears over higher frequencies.

In the previous studies conducted on patients with IBD thusfar, hearing loss has been determined using PTA. Although in these patients, the most important reason for hearing loss is believedto be cochlear damage due to immune mechanisms, cochlear functions were not analyzed in detail. Apart from the study by Sagit et al. [18] who examined inner ear involvement in adults with IBD, no other study tested DPOAE, which is accepted as the best indicator of cochlear functions [18]. Our study is the first in pediatric population with IBD because we assessed hearing loss using PTA and HFA, and additionally, we analyzed cochlear functions using DPOAE. DPOAE responses are highly correlated with the functions and physiologic movements of the outer hair cells of the cochlea. A normal DPOAE response highly suggests normal cochlear functions [32].

In the study by Sagit etal. [18] conducted on patients with IBD, it was found that DPOAE amplitude levels were significantly lower in patients than those in controls except at 6,000 Hz. They concluded that patients with UC had lower physical movement of outer hair cells thancontrols, and the simultaneous existence of low DPOAE levels and normal PTA results in patients with UC may be an early finding of cochlear involvement. Süslü et al. [12] found that the physical movements of outer hair cells were significantly lower in patients with Behcet's disease than in controls. They attributed their results to the lower rates of SNR in the patients than in the controls. They underlined that the coexistence of low DPOAE responses andnormal hearing thresholds may predict early subclinical cochlear involvement.

In our study, we assessed hearing thresholds using PTA, DPOAE, and SNR at high frequencies also. Forthe whole study population, the mean PTA results were normal. The remaining results showed that pediatric patients with IBD have hearing loss over higher frequencies. The low SNR value is considered to be one of the reliable indicators of cochlear involvement [33]. In this study, no significant difference was found between DPAOE amplitudes between the patients with IBDand controls, but SNR1400, SNR2000, and SNR4000 Hz values were significantly higher for the patient groupthan those for the control group. One of the etiopathological factors as vasculitis in IBDis that the involvement of cochlear vessels may induce cochlear pathology, and this pathology may cause hearing loss. Thus, we recommend hearing function tests at regular intervals without waiting for the presence of hearing loss in children with IBD.

We included both UC and CD into the same group as IBD. One of the reasons is that these two illnesses share most common pathophysiologic pathways and manifestations. Thus, it is not always possible to distinguish these two, especially in the early diagnostic periods. Moreover, we realized that most of the previous research on this topic had chosen the same analytic method (combining these two diseases in IBD title) that we have performed.

This studyhas many limitations. First, this is a single-center study involving limited number of patients. Second, we did not conduct any subanalysis to assess the difference between patients with UC and CDowing to the limited number of patients. Third, a long observational period with multiple periodic audiological tests showing progressive SNHLs should give more comprehensive information [8]. Furthermore, response to steroids and other immunosuppressive therapies would be a strong diagnostic indicationfor SNHL in children with IBD [8]. Fourth, a diagnostic blood test detecting antibodies against 68-kD-protein in inner ear antigens might be another strong indicationfor the qualitative difference between the 2 groups [8], but unfortunately it was unavailable. Finally, three-dimensional magnetic resonance imagingmay play a limited diagnostic role revealing the obliteration of the inner ear [8]. However, we did not have this imaging modality.

CONCLUSION

We showed that SNHL in pediatric patients with IBD was seen at the high frequencies. It could represent a potential early indicator of SNHL in this population. This has to be substantiated with follow-up audiograms. Although no hearing loss is clinically prominent, we recommend assessing the hearing function tests at regular intervals in this population. Thus, a higher clinical suspicion for hearing loss is required for this population. We recommend hearing function tests twice in a year for early diagnosis. HFA and DPOAE can be used safely in this population for monitoring the hearing loss.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.K., E.P., Z.Ç.; Design – G.K., E.P., Z.Ç.; Supervision – E. P., G. K., Ö.Y.; Resource –E.P., G.K., Z.Ç.; Materials – E.P., Z.Ç., M.T., T.A., E.A.; Data Collection and/or Processing – E.P., T.A., Z.Ç.; Analysis and/or Interpretation – E.P., G.K., Z.Ç.; Literature Search – E.P., Z.Ç., M.T.; Writing – E.P., G.K., Z.Ç.; Critical Reviews – E.P, G. K, Z. Ç., Ö.Y.

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

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

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