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## Sensorineural hearing loss in pediatric celiac patients

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### ABSTRACT

**Objective:** Celiac disease (CD) is an immune-mediated chronic inflammatory gluten-dependent intestinal disease affecting 0.5–1% of the general population worldwide. CD is underdiagnosed even with sophisticated health care; approximately 10% of people affected by CD are now diagnosed. The recognition of the atypical extra-intestinal manifestations, including neurological disorders increased the diagnosis of CD. At present, no data are available on the presence of sensorineural hearing loss in pediatric CD patients. The aim of this study was to determine the incidence and severity of sensorineural hearing loss (SNHL) in different frequencies in pediatric CD patients.

**Methods:** A sample of 32 biopsies and serologically proven newly diagnosed pediatric CD patients (CD group) (64 ears) and 32 sex and age-matched healthy subjects (64 ears) as control group (C group) were included in this study. Anthropometric measurements, physical examinations including ear nose and throat and pure-tone audiometry at frequencies 250–8000 Hz were performed in all subjects in both groups. Slight/mild SNHL was defined as a loss of detection of sound within the 16–40 dB range. The mean age of patient and control group was 11.9 and 11.3, respectively ( $p > 0.05$ ).

**Results:** In CD group, sensorineural hearing loss was found in 13 (40.6%) patients (group A) as it was bilateral in six and unilateral in seven patients. In control group (group C), slight/mild SNHL was found in one (3.1%) subject. The frequency of hearing loss was significantly higher in CD group than in group C ( $p < 0.001$ ).

**Conclusion:** The present study showed a higher prevalence of sensory neural hearing loss in pediatric celiac patients than in healthy controls, suggesting an association between CD and SNHL. The findings of this study suggest that hearing impairment should be searched in newly diagnosed pediatric CD patients. Further longitudinal investigations on a larger sample size will be necessary to confirm the present data and to search the immunological processes which could be the basis of the association between CD and SNHL.

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### 1. Introduction

Celiac disease (CD) is a genetically determined immune-mediated enteropathy triggered by the ingestion of gluten. Celiac disease is one of the most common lifelong disorders affecting around 1% of the general population all over the world [1]. Typical findings of CD are manifested as chronic diarrhea, failure to thrive and abdominal complaints. CD is a multisystemic disease and also associated with atypical/extraintestinal findings such as short stature, anemia, liver dysfunction, osteoporosis, infertility, dental enamel defects, aphtous stomatitis and other autoimmune disorders

[1–3]. Recent studies demonstrated that nervous system impairment in CD is more common and variable than previously reported and could be regarded as one of the most frequent extraintestinal presentations [4,5]. A diversity of neurologic disorders such as hypotonia, peripheral neuropathy, developmental delay, learning disorders, attention deficit hyperactivity disorder, cerebellar ataxia, epilepsy, migraine, headache and night blindness are also accepted to be among the extraintestinal findings of CD [3–5].

Sensorineural hearing loss (SNHL) is a neurological condition that may result in negative effects on speech and language acquisition, social, emotional and academic development deficits [6,7]. In US National Health and Nutrition Examination Survey (NHANES) III, bilateral SNHL prevalence has been found between 1.5 and 3% of normal school-aged children [8].

Histologically proven involvement of cerebellum in CD was first described in an adult postmortem study and in other animal and

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adult studies. This involvement was proposed to be associated with autoimmunity resulting from interaction of antibodies related to CD and nervous system proteins and cells, such as synapsin, Purkinje cells, gangliosides [9–12]. We hypothesized that central or peripheral hearing pathways could be affected by similar autoimmune mechanism in pediatric CD patients.

The prevalence of subclinical sensorineural hearing loss (SNHL) associated with celiac disease has been investigated in only two adult studies with conflicting results [13,14]. The prevalence and severity of such SNHL in children with CD are not known, yet. The aim of this study is to determine the presence, prevalence and severity of SNHL in children with CD.

## 2. Materials and methods

We conducted a case-control study with a total of 64 subjects. A cohort of 32 serology and biopsy-proven pediatric CD patients (64 ears) who were diagnosed in pediatric gastroenterology department and healthy age and sex matched 32 control subjects (64 ears) were included in the study. Otologic status was assigned based upon history, examination findings and audiologic evaluation. Detailed information was obtained about possible etiological factors leading to hearing loss such as intrauterine infection, perinatal hypoxia, exposure to ototoxic drugs and noise, ear surgery, tympanic membrane perforation, history of head trauma, metabolic diseases and having a relative with hearing loss. There were no subjects who had had a history of any of these factors. Participants were excluded from the study if they had any of the following: (1) otoscopic evidence of a perforated tympanic membrane or other middle ear pathology, (2) presence of a flat tympanogram or absence of acoustic reflexes at 1 kHz with contralateral stimulation, or (3) an air-bone gap of 5 dB at any frequency.

### 2.1. Audiometry and middle ear evaluation

The initial hearing examination has been made at the time of diagnosis of CD before starting the dietary treatment and included otoscopy, tympanometry, pure-tone air- and bone-conduction threshold measurements, and speech audiometry. Pure-tone audiometry was performed at frequencies of 250, 500, 1000, 2000, 4000, 8000 Hz using the diagnostic audiometer (Madsen orbiter 922-2 Clinical Audiometer, Denmark) in a sound-treated cabin. Tympanometric measurements were done using a TDH-39 headset and Middle Ear Analyzer (TympStar GSI, Grason-Stadler Inc., Milford, USA). On immittance, all participants had a normal peak compliance, peak pressure, gradient and ear canal volume, and acoustic reflex, as defined by American Speech Language and Hearing Association.

Slight/mild hearing loss was described as detection of sound within the 16–40 dB range, moderate hearing loss within 41–65 dB, severe hearing loss within 66–95 dB, and profound hearing loss at 96 dB and above [7,8,15,16].

This research was performed in accordance with the principles of the Declaration of Helsinki, and approval for this study was granted by the local ethics committee. Informed consent was obtained from all participants/relatives.

**Table 2**  
Sensory neural hearing loss characteristics of CD and control group.

	Sex/age (years)	Severity of SNHL	Bilateral SNHL	Unilateral SNHL	Unilateral SNHL (side)	SNHL frequency
CD (n = 13)	12 Female, 1 Male, (11.8)	All slight/mild	6/13	7/13	5 left, 2 right	5 high & low, 8 low
Control (n = 1)	1 Male, (15)	Slight/mild	1/1	–	–	Low

**Table 1**  
Prevalence of slight/mild SNHL in CD and Control group.

	CD (n = 32, 64 ears)	Control (n = 32, 64 ears)	p
Slight/mild SNHL n (%)	13 (40.6)	1 (3.1)	<0.0001

### 2.2. Statistical analyses

The statistical analyses were performed using SPSS 16.0 for Windows. Chi-square test was used to compare CD and control groups regarding gender. The normality of the audiologic variables was analyzed by Kolmogorov–Smirnov test. Student *t* test, Kruskal–Wallis tests, and Mann–Whitney *U* tests were used for comparing affected CD group (group A), unaffected CD group (group U) and control group (group C) regarding the averages. *p* Value lower than 0.05 was required for statistical significance.

## 3. Results

The mean age of patients with CD was  $11.9 \pm 2.5$  years (range 7–15 years); 23 were female and 9 were male patients. The mean age of control group was  $11.3 \pm 2.7$  years (range 7–16 years); 17 were female and 15 were male subjects. There was no statistically significant difference between the ages and genders of the CD and control groups ( $p > 0.05$ ). There was no statistically significant difference between the ages of group A ( $n = 13$ ), group U ( $n = 19$ ) and C ( $n = 31$ ) (mean age;  $11.8 \pm 2.8$ ,  $12 \pm 2.3$  and  $11.3 \pm 2.3$ , respectively,  $p > 0.05$ ). One subject from control group who was affected was excluded from comparison of three groups. Otoscopic examination was normal in all participants.

In CD group, slight/mild sensorineural hearing loss was found in thirteen (40.6%) patients (affected CD group, group A) and 19 CD patients had normal hearing (unaffected CD group, group U). Hearing loss was bilateral in six and unilateral in seven patients in group A. In control group (group C) slight/mild SNHL was found in one (3.1%) subject (Tables 1 and 2). The frequency of hearing loss was significantly higher in CD group than in group C ( $p < 0.0001$ ). Speech discrimination was also lower in CD than group C ( $97.1 \pm 3.5$  vs  $99 \pm 2$ , respectively,  $p < 0.05$ ). Kruskal–Wallis analysis for comparison of ear pure-tone threshold levels of groups A, U and C revealed that there was a significant difference among these groups at left at 250 and 500 Hz and at right at 250, 500 and 8000 Hz frequencies (Tables 3 and 4).

Normal peak compliance, peak pressure, gradient, ear canal volume and acoustic reflexes were obtained by immittance measures in the patients and controls. Because there was no air-bone gap in the participant, only air conduction thresholds were taken into consideration.

## 4. Discussion

For the first time in pediatric literature to our best knowledge, we observed significantly higher prevalence (40.6%) of sensorineural hearing loss in children with CD than control subjects. This finding suggests that there is an association between CD and sensorineural hearing loss in pediatric cases. Despite the presence

**Table 3**

Left ear pure tone audiometric findings of subjects.

Frequency (Hz)	Group A left ear (n=13)	Group U left ear (n=19)	Group C left ear (n=31)	p
250	20 (10–25)	10 (5–15)	10 (0–30)	0.0001 <sup>#,*</sup>
500	15 (5–15)	10 (0–15)	5 (0–15)	0.001 <sup>#,**</sup>
1000	5 (0–15)	5 (0–10)	5 (0–15)	NS <sup>#</sup>
2000	5 (0–15)	5 (0–15)	5 (0–15)	NS <sup>#</sup>
4000	5 (0–25)	5 (0–15)	5 (0–20)	NS <sup>#</sup>
8000	10 (0–25)	5 (0–20)	5 (0–15)	NS <sup>#</sup>
SDS %	96 (88–100)	100 (92–100)	100 (92–100)	NS <sup>#</sup>

Values (Pure tone audiometry result as dB) are median (range) unless otherwise indicated.

NS, not significant, group A, CD affected group, group U, CD unaffected group, group C, Control group. SDS, speech discrimination score.

<sup>#</sup> Kruskal–Wallis tests.<sup>\*</sup> Group A vs U,  $p=0.0001$ , group A vs C,  $p=0.0001$ , group U vs C,  $p=0.374$  (NS).<sup>\*\*</sup> Group A vs U,  $p=0.0001$ , group A vs C,  $p=0.0001$ , group U vs C,  $p=0.514$  (NS).**Table 4**

Right ear pure tone audiometric findings of subjects.

Frequency (Hz)	Group A right ear (n=13)	Group U right ear (n=19)	Group C right ear (n=31)	p
250	15 (10–30)	10 (0–15)	10 (0–20)	0.0001 <sup>#,*</sup>
500	10 (0–30)	10 (0–15)	5 (0–15)	0.02 <sup>#,**</sup>
1000	5 (0–30)	5 (0–15)	5 (0–15)	NS <sup>#</sup>
2000	5 (0–25)	5 (0–15)	5 (0–15)	NS <sup>#</sup>
4000	5 (0–15)	5 (0–15)	5 (0–15)	NS <sup>#</sup>
8000	15 (0–35)	5 (0–15)	5 (0–15)	0.018 <sup>#,***</sup>
SDS %	96 (84–100)	100 (88–100)	100 (92–100)	NS <sup>#</sup>

Values are median (range) unless otherwise indicated.

NS, not significant, group A, CD affected group, group U, CD unaffected group, group C, control group.

<sup>#</sup> Kruskal–Wallis tests.<sup>\*</sup> Group A vs U,  $p=0.0001$ , group A vs C,  $p=0.0001$ , group U vs C,  $p=0.374$  (NS).<sup>\*\*</sup> Group A vs U,  $p=0.018$ , group A vs C,  $p=0.012$ , group U vs C,  $p=0.893$  (NS).<sup>\*\*\*</sup> Group A vs U,  $p=0.016$ , group A vs C,  $p=0.01$ , group U vs C,  $p=0.968$  (NS).

of hearing loss, none of the CD patients complained of hearing impairment. Our findings suggest that since insidious hearing loss may result in a decrease in socioemotional and behavioral development, specific areas of cognitive development, and sensory-motor development, early detection is crucial [17]. Our findings support the hypothesis that immune-related pathology would be responsible for the involvement of inner ear for the development of slight/mild SNHL in pediatric CD. And CD related SNHL may be a causative link between CD and learning disability and attention deficit hyperactivity disorder attributed to CD [4]. Our data suggest that there is a need for hearing loss screening at the time of diagnosis in pediatric celiac patients.

Although CD is affecting around 1% of the population worldwide, there are no accurate estimates of the prevalence of the neurological manifestations of gluten sensitivity in the general population since most of the CD patients with neurologic symptoms present to neurology clinics. Up to 22.5% in adults and up to 24.5% in children for the prevalence of neurological dysfunction among patients with biopsy proven classic CD has been reported from gastrointestinal clinics [1,18,19]. The mechanism of neural tissue involvement proposed to be associated with autoimmunity resulting from interaction of antibodies related to CD and nervous system proteins and cells and the central or peripheral hearing pathways could be affected by the similar mechanisms in pediatric CD patients which may be leading to SNHL [9–11].

The triggering autoimmune factor for the pathogenesis of inner ear pathology remains to be established. Several hypotheses had been postulated to explain the basis of association of CD with sensorineural hearing loss such as impaired nutrient and vitamin absorption (such as Vit B12, folate, vitamin D, E, pyridoxine and biotin) [20,21], cerebral vasculitis [22], the existence of antineuronal antibodies, invasion of activated lymphocytes into the labyrinth, immune complex deposition that leads to tissue injury [23,24], and immunopathology leading to inner ear immune

response. There is a continuous recirculation of immuno-competent cells in this area of the inner ear. The endolymphatic sac plays an integral function for inner ear immune response since it is the only site which contains and recirculates immuno-competent cells within the inner ear [25]. Endolymphatic sac is producing interleukin-2 which regulates the immune response. IL-2 activation of endothelial cells of the spiral modiolar vein potentiates the intercellular adhesion molecule-1 expression which recruits more leucocytes from the bloodstream and potentiation of immune response resulted [26,27].

Since the immunopathogenesis of CD is multifactorial sensorineural hearing loss pathogenesis associated with pediatric CD may be multifactorial also. Type II and III immunological reactions would be causing inner ear pathology together in pediatric CD patients [28,29]. In type II reaction, an immunoglobulin directed against a tissue or organ is basic mechanism for injury of endolymphatic sac as in the pathogenesis of Meniere's disease and in type III reaction an immune complex deposition leads to inner ear pathology as in the pathogenesis of Wegeners granulomatosis [24]. Pratesi et al. demonstrated in vitro that antiendomysial antibodies immunofluoresce with cerebral vasculature [30]. Autoimmune activation against transglutaminase in brain vascular endothelium can therefore be postulated. This phenomenon might give rise to facilitation of autoimmune mechanism activation within the central nervous system [22]. Further studies were warranted in order to confirm and explain the immune mechanism of inner ear pathology in pediatric CD especially association endolymphatic sac response.

SNHL frequency in CD group was higher than that in control group (Table 1). Control group SNHL frequency was consistent with literature findings [8]. 46% of these cases with SNHL had bilateral and the others were unilateral hearing loss (Table 2).

When hearing losses were evaluated on the basis of frequency in pure tone audiometry, auditory dysfunction was observed

mostly at lower frequencies of 250 and 500 Hz. These findings may suggest that although auditory dysfunction was detected at lower frequencies, it may lead to important speech discrimination disabilities. Speech discrimination problems in children may cause language regression and deceleration of linguistic, academic and social development. Hearing loss frequency at 8000 Hz was also detected in right ear of our CD group. Leggio et al. had detected that hearing loss frequencies of 70% of adult CD patients were high [13]. Our findings suggest that hearing impairment of pediatric CD patients may be at low and also at high frequencies with a slight tendency towards low frequencies.

This study may have a limitation because of the small size. Given this, our findings should only be viewed as preliminary. A further larger scale study is needed to definitively determine whether there is an association between pediatric CD and SNHL. And this future study may involve the long-term follow up in order to check reversibility of inner ear pathology with the dietary treatment of CD.

As a conclusion, SNHL seems to be representing an extra-intestinal neurological manifestation of CD in children. Children with CD could not be aware of hearing deficiency and not in complain about hearing loss but language and speech discrimination regression may be developing, may be leading to learning disabilities [6]. This preliminary study findings suggest that hearing loss should be searched in newly diagnosed pediatric CD patients but larger scale studies needed for deciding about real necessity of routine hearing function tests. Audiometric tests give information about whole process of hearing and cannot differentiate pathological step that was affected. In the topic of CD related SNHL, which step of hearing is affected remains to be determined in further studies searching the pathological mechanism of SNHL in children with CD.

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