Sensorineural hearing loss and celiac disease: A coincidental finding

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U Volta, GG Ferri, R De Giorgio, et al. Sensorineural hearing loss and celiac disease: A coincidental finding. Can J Gastroenterol 2009;23(8):531-535.

BACKGROUND: Celiac disease (CD) can be associated with a variety of extraintestinal manifestations, including neurological diseases. A new neurological correlation has been found between CD and sensorineural hearing loss (SNHL).
OBJECTIVE: To verify the association between SNHL and CD, and to establish whether the neurological hearing impairment in CD is related to nonorgan-specific and antineuronal antibodies, as well as the presence of autoimmune disorders.
METHODS: A sample of 59 consecutive biopsy- and serologically proven CD patients were studied. Among CD patients, 11 were newly diagnosed and 48 were on a gluten-free diet. Hearing function was assessed by audiometric analysis in all CD patients as well as in 59 age- and sex-matched controls. Patients were tested for a panel of immune markers including nonorgan-specific autoantibodies and antineuronal antibodies.
RESULTS: SNHL was detected in five CD patients (8.5%) and in two controls (3.4%). In one patient, the SNHL was bilateral, whereas the remaining four had a monolateral impairment. The prevalence of SNHL was not significantly different between CD patients and controls. At least one of the antibodies tested for was positive in two of the five CD patients with SNHL and in 12 of the 54 CD patients without SNHL. Antineuronal antibodies to central nervous system antigens were consistently negative in the five CD patients with SNHL. Only one of the five CD patients with SNHL had Hashimoto thyroiditis.
CONCLUSIONS: SNHL and CD occur coincidentally. Hearing function should be assessed only in CD patients with clinical signs of hearing deficiency.

Key Words: *Antineuronal antibodies; Autoimmunity; Celiac disease; Neurological disorders; Sensorineural hearing loss*

Surdité de perception et maladie cœliaque : relation concomitante

CONTEXTE : La maladie cœliaque (MC) peut être associée à différentes manifestations extraintestinales, notamment à des affections neurologiques. Une nouvelle corrélation neurologique a été découverte entre la MC et la surdité de perception (SP).
BUTS : L'étude avait pour buts de vérifier le lien entre la SP et la MC et de déterminer si l'hypoacousie neurologique dans la MC était liée à des anticorps non spécifiques d'organe et à des anticorps antineuronaux, ainsi qu'à la présence de troubles auto-immuns.
MÉTHODE : Cinquante-neuf malades consécutifs, chez qui la MC avait été confirmée par biopsie et par analyses sérologiques ont fait l'objet d'examens. La maladie avait été diagnostiquée depuis peu chez 11 d'entre eux, et 46 patients suivaient un régime sans gluten. Il y a eu examen audiométrique chez tous les patients souffrant de MC ainsi que chez 59 témoins appariés selon l'âge et le sexe. Les malades ont été soumis à une série de marqueurs immunitaires, y compris à la recherche d'autoanticorps non spécifiques d'organe et d'anticorps antineuronaux.
RÉSULTATS : Une SP a été détectée chez cinq patients atteints de MC (8,5 %) et chez deux témoins (3,4 %). Dans un cas, la SP était bilatérale tandis que, dans les quatre autres cas, la SP était unilatérale. La prévalence de la SP enregistrée chez les malades ne différait pas beaucoup de celle enregistrée chez les témoins. Au moins un des anticorps vérifiés s'est révélé positif chez 2 patients sur 5 atteints de MC et de SP et chez 12 patients sur 54 atteints de MC mais exempts de SP. Les anticorps antineuronaux contre des antigènes du système nerveux central se sont tous révélés négatifs chez les cinq patients atteints à la fois de MC et de SP. Un seul de ces cinq patients souffrait d'une thyroïdite d'Hashimoto.
CONCLUSIONS : La SP et la MC existent en concomitance. Seuls les patients atteints de MC et présentant des signes cliniques de SP devraient faire l'objet d'une évaluation audiométrique.

Celiac disease (CD) is an immune-mediated permanent enteropathy caused by the ingestion of gluten-containing foods (1). This food intolerance, which is believed to be very high in the general population (1 in 100 individuals [2,3]), is the result of a complex interplay between intrinsic and extrinsic factors. Different from the majority of other immunological disorders, several studies have investigated the pathogenesis of CD and identified the factors involved, such as the alimentary trigger (eg, gliadin), the close genetic association (human leukocyte antigen [HLA]-DQ2 and/or HLA-DQ8) and the specific autoantigen tissue transglutaminase (tTG) (4). The interaction between gliadin and tTG plays a crucial role in mucosal flattening in the small intestine (5).

Although the target organ is the gut, CD is a typical example of a systemic disorder involving extraintestinal tissues and organs in at least 20% to 30% of patients (6). Because of its ubiquitous distribution in the body, tTG has been suggested to play a role in systemic manifestations related to CD. The

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Received for publication October 17, 2008. Accepted December 1, 2008

upregulation of tTG can explain the wide spectrum of autoimmune and idiopathic manifestations of CD. In particular, the cross-linking of tTG with various bacterial, viral, nutritional and endogenous antigens can lead to a secondary immune response, with an increased risk of autoimmune disorders after many years of gluten exposure (7). The systemic involvement of CD can include the skin, thyroid, pancreas, heart, joints, muscles, bones, reproductive system, liver, peripheral nervous system and central nervous system (CNS) (1). The occurrence of nervous system impairment in CD is well established and should be regarded as one of the most frequent extraintestinal presentations of gluten-sensitive enteropathy. Approximately 10% of patients with CD display neurological symptoms related to a wide array of disorders such as epilepsy, myoclonus, cerebellar ataxia, multifocal leukoencephalopathy, dementia, chorea, migraine, multiple sclerosis, memory/attention impairment, and peripheral axonal and demyelinating neuropathies (8-11). Malabsorption alone (often completely absent) does not explain the pathophysiology and clinical course of most of the associated neurological disorders. An emerging hypothesis is that autoimmunity can act as a mechanism that triggers the neurological dysfunction found in CD. This hypothesis is strengthened by the evidence of lymphocytic infiltration in the CNS and peripheral nervous system, as well as circulating antineuronal antibodies in CD patients with neurological impairment (12).

Recently, a new neurological manifestation was described in a high percentage of CD patients (13). Ten of 24 adult CD patients (41.7%) were found to have sensorineural hearing loss (SNHL) compared with SNHL in only two of 24 healthy controls (8.3%). Despite the small sample size, the finding of SNHL was significantly higher in CD patients than in controls, suggesting the discovery of a new extraintestinal manifestation of CD. Thus, Leggio et al (13) hypothesized that immunological markers, such as nonorgan-specific (NOS) autoantibodies and antineuronal antibodies, could play a role in determining SNHL in CD patients. However, these potentially relevant pathogenetic factors were not investigated in the present study.

The aim of the present study was to establish a possible association between SNHL and CD, and to evaluate the prevalence of SNHL in CD patients compared with healthy control subjects. CD patients included untreated and treated subjects to verify whether SNHL was related to CD activity. Moreover, a thorough investigation of autoimmune markers (eg, NOS autoantibodies and antineuronal antibodies) and associated autoimmune disorders was performed in CD patients to identify a possible correlation between SNHL and the underlying immunological impairment.

METHODS

Study population

The study population included 59 consecutive biopsy-proven CD patients (50 women, nine men; mean age 34 years; range 14 to 49 years of age), diagnosed between January 2005 and December 2007, in the outpatient clinic of the Department of Clinical Medicine, University of Bologna, Bologna, Italy. This sample size represented approximately one-quarter of the total number of patients diagnosed per year in the referral centre. At the time of diagnosis, all 59 patients showed a duodenal histology consistent with a partial or subtotal villous atrophy (lesion type 3b-3c according to the Marsh-Oberhüber classification [14]) and were positive for both endomysial and tTG antibodies (15). The enrolled CD patients included 11 subjects who were newly diagnosed and 48 who were on a gluten-free diet for a mean duration of at least six months (range four months to two years). A detailed clinical history was collected from each patient to exclude secondary causes of hearing loss (HL). Exclusion criteria included diabetes mellitus, cardiovascular diseases, previous audiological or otological diseases, occupational risk factors with exposure to acute or chronic noise, ototoxic drugs, acute/chronic inflammatory/infectious diseases, previous otological surgical procedures, neoplasms and other possible causes of ear disorders inducing HL. Moreover, patients smoking more than 10 cigarettes/day and/or drinking more than 30 g of ethanol/day were also excluded. All subjects provided written informed consent and the study was approved by the local ethics committee in accordance with the Declaration of Helsinki.

The control group included sex- and age-matched healthy subjects (n=59) enrolled among physicians and other staff members of our departments, as well as students and hospital employees. The same exclusion criteria for secondary HL were adopted for the control group. Each control subject tested negative for immunological markers of CD (both endomysial and tTG antibodies).

Assessment of hearing function

After an otoscopic examination to verify the integrity of the tympanic membrane and to rule out earwax, an audiometric evaluation was performed in soundproof rooms according to international rules. In particular, air (125 Hz, 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz and 8000 Hz) and bone conduction (250 Hz, 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz) thresholds were recorded bilaterally. A bone conduction threshold of 25 decibels or more, recorded in two consecutive frequencies, was diagnostic for SNHL. This diagnostic criterion (16) was adopted for two main reasons: the selected threshold values were helpful to detect even mild impairments and the exclusion of monofrequential impairments helped to avoid detecting minor disorders of uncertain origin.

Antibody testing and associated autoimmunity

A routine serum sample for antibody testing was available for all 59 patients at the time of study enrollment. To evaluate the correlation between immunological abnormalities and the presence of SNHL, all 59 CD patients were tested for the following antibodies:

1. NOS autoantibodies (ie, antinuclear [ANA], antismooth muscle, antimitochondrial, anti-liver-kidney microsomal, antireticulin and antiribosomal antibodies analyzed by indirect immunofluorescence on rodent tissue substrates [rat liver, kidney and stomach]) (17);
2. ANA on HEp2 cells assessed by indirect immunofluorescence classifying the different ANA patterns (speckled, nucleolar, homogeneous and membranous) (18); and
3. Antineuronal antibodies directed against the CNS on monkey and rat cerebellum substrates and against the enteric nervous system (ENS) on rat ileum and colonic substrates. The pattern of antineuronal antibodies to the CNS is

characterized by cytoplasmic or nuclear positivity in Purkinkje cells and by nuclear staining of granular layer neurons in the cerebellum. Antineuronal antibodies to the ENS result in a bright cytoplasmic fluorescence detectable in ganglion cell bodies of the myenteric (Auerbach's) and submucosal (Meissner's) plexuses (12).

In addition, sera obtained from the 59 healthy controls were tested for the previously listed panel of autoantibodies. The presence of autoimmune disorders was investigated to verify whether SNHL in CD patients was related to the coexistence of a wider abnormality of the immune system.

Statistical analysis

The two-tailed Fisher's exact test was used to compare the prevalence of SNHL in CD patients with the prevalence in healthy controls, to evaluate any difference of SNHL prevalence in untreated and treated CD patients, and to establish any correlation between the finding of SNHL, immunological markers (NOS autoantibodies, ANA and antineuronal antibodies) and associated autoimmunity. Differences were considered statistically significant at $P<0.05$.

RESULTS

A mild high-frequency SNHL was detected in five of the 59 CD patients studied (8.5%) and in two of the 59 healthy controls (3.4%) (Table 1). Although the prevalence of SNHL was slightly higher in CD patients than the control group, the difference was not statistically significant (P=0.219). In one CD patient, SNHL was bilateral, whereas the remaining four had a monolateral impairment. The prevalence of SNHL did not significantly differ between untreated (0 of 11) and treated CD patients (five of 48 [10.4%]; P=0.342). At least one of the antibodies tested (NOS autoantibodies, ANA and antineuronal antibodies) was positive in two of the five CD patients with SNHL and in 12 of the 54 CD patients without SNHL. In particular, antineuronal antibodies to CNS antigens were consistently negative in the five CD patients with SNHL, whereas they were detected in four CD patients with normal hearing function. Antineuronal antibodies to ENS antigens were positive in one CD patient with SNHL and in two CD patients without hearing impairment. None of the antibodies tested were positive in the two healthy controls with SNHL, whereas five of the 57 healthy controls without SNHL were positive for at least one antibody (8.7%) (three for NOS and two for ANA). Antibodies to CNS and ENS antigens were consistently negative in the healthy control group. Regardless of SNHL, the prevalence of antineuronal antibodies in CD patients versus controls was statistically significant (P=0.006). Only one of the five CD patients with SNHL displayed an associated autoimmune disorder (Hashimoto thyroiditis) compared with an associated autoimmune disorder (Hashimoto thyroiditis, connective tissue disease, atrophic gastritis and pernicious anemia) in eight of the 54 CD patients without SNHL. SNHL detected in CD patients did not result in a statistically significant relationship with immunological markers and autoimmune disorders (Table 2). Clinical data, antibody markers and associated autoimmune disorders of the five CD patients with SNHL are summarized in Table 3.

TABLE 1
Prevalence of sensorineural hearing loss (SNHL) in celiac disease patients and healthy controls

	Celiac disease			
	All (n=59)	Untreated (n=11)	Treated (n=48)	Healthy controls (n=59)
SNHL, n (%)	5 (8.5)	0 (0)	5 (10.4)	2 (3.4)

SNHL in all versus healthy controls P=0.219. Untreated versus treated P=0.342 (two-tailed Fisher's exact test)

DISCUSSION

HL affects the general population with a non-negligible prevalence (19) and is frequently associated with aging (20). The prevalence of SNHL is approximatley 9% in the general population of the United States (20). The etiopathogenetic mechanisms involved in HL are linked to a series of possible diseases of the external, middle and inner ear. While hypoacusia originating from the external and middle ear is responsible for a conductive hearing loss, diseases of the cochlea and its neural pathways are the cause of SNHL, which recognizes a variety of etiological factors including presbyacusis, acute/chronic noise-induced HL, ototoxicity, Méniere's disease, sudden HL and benign tumours. Moreover, immune-mediated SNHL has also been reported because various immunological markers such as rheumatoid factor, heat shock protein, ANA and antiphospholipid/anticardiolipin, as well as antithyroid antibodies are involved in the pathogenesis of some CD patients with SNHL (21,22). SNHL was recently recognized by Leggio et al (13) as a possible new disorder occurring in approximately one-half of CD patients. CD is currently regarded as an autoimmune

TABLE 2
Autoimmune markers and associated autoimmune disorders in celiac disease (CD) patients with and without sensorineural hearing loss (SNHL)

	Autoimmune markers: NOS, ANA, antineuronal antibodies to CNS and ENS: Positivity for at least one antibody	Associated autoimmune disorders: Hashimoto thyroiditis, connective tissue disorders, atrophic gastritis and pernicious anemia
CD with SNHL	2/5 (40)	1/5 (20)
CD without SNHL	12/54 (22.2)	8/54 (14.8)
Healthy controls with SNHL	0/2 (0)	0/2 (0)
Healthy controls without SNHL	5/57 (8.7)	0/57 (0)

Data are presented as n/n (%). Autoantibodies as a whole (nonorgan-specific autoantibodies [NOS], antinuclear antibodies [ANA] and antineuronal) in celiac patients (with and without SNHL) versus healthy controls (with and without SNHL) P=0.021. Autoimmune markers in celiac patients with SNHL versus celiac disease patients without SNHL P=0.339. Associated autoimmune disorders in celiac patients with SNHL versus celiac patients without SNHL P=0.576. CNS Central nervous system; ENS Enteric nervous system

TABLE 3
Clinical data, antibody markers and associated autoimmune disorders in the five celiac disease patients with sensorineural hearing loss (SNHL) and SNHL characteristics

Sex, age (years)	Gluten-free diet, months	Degree of SNHL	Mono- or bilateral SNHL, side	SNHL frequency	NOS Abs	ANAs	Antineuronal antibodies	Autoimmune disorders
Male, 44	24	Mild	Monolateral, left	High	Negative	Negative	Negative	None
Female, 49	15	Mild	Monolateral, left	High	Negative	Negative	Negative	None
Female, 43	16	Mild	Monolateral, left	High	Negative	Negative	ENS+	Hashimoto thyroiditis
Female, 43	18	Mild	Monolateral, left	High	Negative	Negative	Negative	None
Female, 42	12	Mild	Bilateral	High	SMAv+	ANAs+	Negative	None

ANAs Antinuclear antibodies – speckled pattern; ENS Enteric nervous system; NOS Abs Nonorgan-specific autoantibodies; SMAv Antismooth muscle antibodies – vascular pattern

disorder that primarily targets the small bowel, with a wide spectrum of associated extraintestinal manifestations (1,6). One of the most common tissues involved in CD is the CNS, with various clinical manifestations among which gluten ataxia and peripheral neuropathy are the most frequent (8-12). These neurological disorders occurring in CD patients are likely immune-mediated as suggested by the high prevalence of antiganglioside, as well as antineuronal antibodies and other immune markers found in CD patients with neurological involvement (23-26). The present study was designed with two main purposes: to further expand the possible association between CD and SNHL by examining a greater number of CD patients than the sample size evaluated by Leggio et al (13), and to establish the possible role of autoimmunity in the development of SNHL in CD. Our results do not support a correlation between SNHL and CD, suggesting that the identification of SNHL and CD in the same patient should be considered coincidental rather than due to an actual association. Moreover, the hypothesis that abnormalities of the immune system can be responsible for the involvement of the inner ear causing SNHL is unlikely because the prevalence of antineuronal antibodies to CNS, NOS autoantibodies and ANA was not higher in CD patients with SNHL than the prevalence of the same autoantibodies in CD patients without SNHL. The prevalence of autoantibodies in the healthy control group was consistent with that previously reported in the literature (12,27). Moreover, the finding of SNHL in CD patients was not associated with an increased prevalence of autoimmune disorders such as autoimmune thyroiditis, connective tissue disorders and atrophic gastritis. Overall, the finding of a neurological involvement of the inner ear was twice as high in CD subjects than in healthy controls (8.5% versus 3.4%, respectively), a figure that did not reach statistical significance. Thus, an expected association between SNHL and CD would be approximately 20%. Our findings, which show an association in only 8.5% of patients, is well below the expected significant value (ie, comparable to the association found in the general population) (20).

CONCLUSION

Based on a relatively large number of patients, our data suggest that hearing function tests should not be routinely performed in the clinical setting of CD. An assessment of hearing function should be recommended in CD patients with clinical signs of hearing deficiency.

FINANCIAL SUPPORT: This work was supported by the Italian Ministry of University and Research (COFIN Project number 2003064378_003, 2004062155_003) and RFO funds from the University of Bologna to R De Giorgio and G Barbara. R De Giorgio is a recipient of a grant from 'Fondazione Del Monte di Bologna e Ravenna', Bologna, Italy.

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