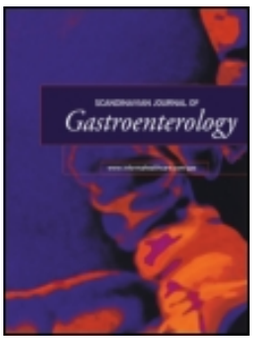

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ORIGINAL ARTICLE

Coeliac disease and hearing loss: Preliminary data on a new possible association

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Abstract

Objective. Coeliac disease (CD), an autoimmune gluten-dependent enteropathy, can be associated with several extra-intestinal manifestations, including neurological disorders. At present, no data are available on the presence of hearing loss disorder in coeliac patients. The aim of the present study was to investigate the prevalence of hearing loss in coeliac patients compared with that in healthy controls. ***Material and methods.*** Twenty-four adult coeliac patients and 24 healthy subjects matched for gender, age, smoking and drinking habits were enrolled in the study. Among the coeliac patients, 6 were newly diagnosed and 18 patients were on a gluten-free diet for at least one year. ***Results.*** A hearing loss was found in 10 (47.1%) coeliac patients and 2 (9.1%) healthy controls. All CD patients with hearing loss presented a sensorineural hearing loss. The prevalence of hearing loss was significantly higher in coeliac patients than in healthy controls ($p = 0.01$) but it was not significantly different between untreated (33.3%) and treated (44.4%) coeliac patients (p: NS). ***Conclusions.*** Despite the low number of subjects evaluated, the present study showed a higher prevalence of hearing loss in coeliac patients than in healthy controls, suggesting an association between CD and hearing loss. Immunological processes such as ear-specific and non-specific autoantibodies and vasculitis could be the basis of this association. Further longitudinal investigations on a larger sample size will be necessary to confirm the present data.

Key Words: *Autoantibodies, coeliac disease, gluten-free diet, hearing loss, immune-mediated mechanisms, vasculitis*

Introduction

Coeliac disease (CD) is an autoimmune, gluten-dependent enteropathy, characterized by subtotal or total atrophy of intestinal villi which improves after introduction of a gluten-free diet (GFD) [1]. Classical clinical features of CD include malabsorption with diarrhoea, steatorrhoea, abdominal distension, flatulence, weight loss, iron-deficiency anaemia, osteoporosis and impaired nutritional status [2–4]. Moreover, CD can be associated with several extra-intestinal manifestations [5]. Among them, neurological disorders have been reported, including epilepsy [6], peripheral neuropathy [7], myoclonus and posterior column demyelination [8], headache [9], cerebellar ataxia [10], brain atrophy and dementia [11]. The aetiopathogenesis of these neurological disorders in CD patients remains uncertain [12], although brain vasculitis [13–15], the presence of anti-neuronal antibodies [16] and regional cerebral blood flow abnormalities [17] have been suggested as possible pathophysiological mechanisms [17,18].

Hearing loss (HL) represents a common disorder in the general population and the two major forms are conductive and sensorineural disorders [19]. Sensorineural HL (SNHL) represents more than 90% of HL [19]. The prevalence of HL increases with age [19,20]. In particular, HL affects about 20% of the population aged from 48 to 59 years and between 25% to 40% of the population aged 65 years or older [19,20]. Abnormalities of the middle and external ear represent the most common causes of conductive HL, while the main cause of SNHL is

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increasing age [19]. However, immune-mediated hearing loss (HL) has been also largely described [21–24].

Since immune-mediated mechanisms could be the basis of both HL and CD-related neurological disorders, an association between CD and HL could be hypothesized. However, at present, no data are available. Consequently, the aim of the present study was to investigate the possible association between HL and CD through a case-control study on the prevalence of HL in coeliac patients compared with that in healthy controls.

Material and methods

Subjects and methods

A total of 76 patients affected by CD and referred to our Institute of Internal Medicine were consecutively considered for eligibility. Diagnosis of CD was based on the positivity of antigliadin (AGA), antiendomysium (EmA) and/or anti-tissue transglutaminase (anti t-TG) antibodies and was confirmed by the histological evidence of subtotal or total duodenal villous atrophy and increased intraepithelial lymphocytes and crypt hyperplasia [1,3]. In the newly diagnosed CD patients, secondary causes of villous atrophy represented exclusion criteria. CD patients on a GFD were symptom free, serum antibodies titres had returned to normal values and duodenal biopsies showed the restoration of normal mucosal morphology. Exclusion criteria included also secondary causes of HL [25]: diabetes, metabolic and endocrine disorders, cardiovascular diseases, ototoxic drugs, brain tumours, previous head trauma, otological surgery, otological infectious and/or neoplastic diseases, Cogan's syndrome and occupational risk factors. Patients smoking more than 10 cigarettes per day and/or drinking more than 25 g ethanol per day were also excluded.

A total of 24 CD patients (22 F, mean age 37.9 ± 11.4) finally satisfied the inclusion criteria. Among them, 6 patients (25%) were newly diagnosed with CD and 18 patients (75%) had been on a GFD for at least one year (range 12–48 months, mean 22.6 ± 16.9). Twenty-four healthy subjects recruited from our University staff and matched for gender, age, smoking and drinking habits were studied as a control group. In the healthy controls, CD was excluded through CD antibody screening.

HL was assessed by pure-tone audiometry (frequencies 125, 250, 500, 1.000, 2.000, 4.000 and 8.000 Hz; ISO standard), speech discrimination testing and impedence audiometry. The following scale of HL degree was used: mild – >20 to 40 dB HL; moderate – >40 to 70 dB HL; severe – >70 to 90 Db HL; profound – >90 dB HL. Tone audiometry has a sensitivity of $\geq$94%, a specificity of between 69% and 80% and a reliability of more than 90% [19,26–29].

All subjects gave their informed consent before enrolment. The study protocol complied fully with the guidelines of the Ethics Committee of the Università Cattolica del Sacro Cuore in Rome, Italy.

Statistical analysis

The χ^2 analysis was utilized to compare the number of subjects with HL in both coeliac patients and healthy controls, the number of untreated and treated coeliac patients with HL and to check for differences between coeliac patients and healthy controls in demographic variables. A p-value of less than 0.05 was considered significant.

Results

Ten (10/24; 47.1%) CD patients and two (2/24; 9.1%) healthy controls showed HL. The prevalence of HL was significantly higher in the CD patients than in the healthy controls ($p = 0.01$) and it was not significantly different between untreated (2/6; 33.3%) and treated (8/18; 44.4%) CD patients (p: NS).

The demographic data and HL characteristics in both CD patients and healthy controls are summarized in Table I. In particular, a mild monolateral SNHL was present in 3 out of 10 CD patients affected by HL (3/10; 30%) and in the two hypoacusic healthy controls (2/2; 100%); a moderate monolateral SNHL was observed in 3 out of 10 hypoacusic CD patients (3/10; 30%); a mild bilateral SNHL was present in 4 out of 10 CD patients with HL (4/10; 40%).

Finally, 7 out of the 10 hypoacusic CD patients (70%) presented a high frequency HL and 3 (30%) a low frequency HL. The two hypoacusic healthy controls (100%) showed a low frequency HL.

Discussion

The present study showed a higher prevalence of HL in CD patients in comparison with healthy controls, suggesting a possible association between CD and HL. In particular, all CD patients with HL presented a SNHL, supporting the hypothesis that SNHL could represent a neurological extra-intestinal manifestation of CD. To the best of our knowledge, this study represents the first report on this possible association.

In CD patients, vasculitis has been reported [5,30–32], and cerebral hypoperfusion [17,33] and

Table I. Demographic and clinical data of both coeliac patients and healthy controls in which sensorineural hearing loss was found.

	Gender	Age	GFD months	HL degree	Mono- or bilateral of SNHL	HL frequency
Coeliac patient 1	F	61	0	Mild	Monolateral (L)	High
Coeliac patient 2	F	31	0	Mild	Monolateral (R)	High
Coeliac patient 3	F	34	24	Mild	Monolateral (R)	Low
Coeliac patient 4	F	63	12	Mild	Bilateral	High
Coeliac patient 5	F	28	18	Mild	Bilateral	High
Coeliac patient 6	F	44	18	Mild	Bilateral	High
Coeliac patient 7	F	32	48	Mild	Bilateral	High
Coeliac patient 8	F	58	24	Moderate	Monolateral (R)	High
Coeliac patient 9	M	40	48	Moderate	Monolateral (R)	Low
Coeliac patient 10	F	45	21	Moderate	Monolateral (R)	Low
Healthy control 1	M	23	–	Mild	Monolateral (R)	High
Healthy control 2	F	39	–	Mild	Monolateral (L)	High

Abbreviations: GFD = gluten-free diet; HL = hearing loss; SNHL = sensorineural hearing loss; R = right; L = left.

immune-mediated vasculitis of the central nervous system [13–15] have been described as possible causes of neurological disorders in these patients. On this point, immune-mediated mechanisms acting as triggers in CD extra-intestinal manifestations as thyroid disorders [34], diabetes [35], liver diseases [36–38] and skin disorders [32,39] could be the basis of the possible association between HL and CD. In fact, although immune-mediated HL is a clinical entity that is widely discussed and described [40], several immune-mediated mechanisms including autoantibodies, autoreactive T cells and immune-complex deposition have been suggested as possible mechanisms at the basis of HL [40]. It has been showed that antinuclear antibody (ANA) [41,42], antiphospholipid/anticardiolipin antibodies, anti-thyroid antibodies, rheumatoid factor (RF) [42] and heat-shock protein (HSP) [43,44] are involved in the pathogenesis of a subgroup of HL. Interestingly, several of these antibodies have been reported in CD and/or gluten sensitivity, including ANA [45], antiphospholipid/anticardiolipin antibodies [46–48], anti-thyroid antibodies [45,49,50], RF [51] and HSP [52,53].

Finally, further factors could also influence the possible association between CD and HL, representing common features of both clinical conditions such as thrombophilic conditions [4,54] and hypofolataemia [2,55,56].

With regard to the lack of difference between newly diagnosed CD patients and those on a GFD with respect to HL, in the present study we were unable to address whether differences really do exist, because of the low number of newly diagnosed CD patients enrolled. The effects of GFD on HL as well as on different extra-intestinal disorders related to CD [5] remain to be determined.

In conclusion, our preliminary data show that SNHL could represent a new neurological extra-intestinal CD manifestation. Several immunological mechanisms could represent the link to this possible association. Future studies on a larger sample size also investigating immunological parameters (i.e. ear-related or other anti-neuronal antibodies) are needed to confirm the present observation. If the present observation were confirmed, the possible presence of CD in HL patients with a possible immune-mediated pathogenesis should be investigated.

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