Journal Of Otolaryngology: Research

SCIENTIFIC LITERATURE

Special Issue Article "Menière's Disease"

Research Article

The Humoral Responses to Wheat Antigens in Menière's Disease

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ARTICLE INFO

Received Date: June 03, 2022
Accepted Date: June 23, 2022
Published Date: June 24, 2022

KEYWORDS

Gluten
Celiac disease
Antibodies
Ménière's disease
Vertigo

Citation for this article: Federica Di Berardino, Luca Elli and Diego Zanetti. The Humoral Responses to Wheat Antigens in Menière's Disease. Journal Of Otolaryngology: Research. 2022; 4(1):137

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ABSTRACT

Objectives: Aim of this study was to investigate the humoral immune responses to wheat antigens and related antibodies in MD patients.

Methods: We assessed the reactivity of sera against a repertoire of 51 antigens usually associated with immune reaction to gluten from 28 patients with definite unilateral MD and 100 healthy controls.

Results: MD patients showed an increase of anti-wheat IgA, anti-cerebellar peptide IgA and anti-glutamic acid decarboxylase 65 (GAD 65) IgM compared to healthy controls. In particular, the increase of anti-wheat IgA and GAD 65 IgM has been confirmed in a subgroup of MD patients symptomatically responding to a Gluten Free Diet (GFD).

Conclusion: In MD patients, a general increase of the antibody production against gluten biomarkers was observed; in particular, anti-wheat IgA seems to be associated with clinical response to GFD. However, none of the studied biomarker resulted disease-specific, i.e. it cannot be used as a stand-alone tool for detecting the association between gluten-related disorders and MD.

INTRODUCTION

Gluten is the main structural protein in wheat and other cereals (such as barley, rye and spelt); it is insoluble in water and sodium chloride and it can be further subdivided on the basis of the alcohol solubility between gliadins (alcohol soluble) and glutenins. When mixed with water, gluten creates a three-dimensional network, giving dough the typical elasticity and viscosity [1]. The monomeric gliadins comprise the ω-, α-, and γ- gliadins, based on their mobility on electrophoresis at low pH, while the polymeric types include high molecular weight and low molecular weight subunits of glutenins that are linked by intermolecular disulphide bonds [2]. The interplay between gluten components and the immune system, and its direct cytotoxic effects exerted during the intestinal transit constitute the basis of the so-called Gluten-Related Disorders (GRD) [3]. GRD is an umbrella term including gastrointestinal, neurological and skin disorders. Following the London classification, GRD are further subdivided on the basis of their etiopathogenesis: autoimmune (Celiac Disease [CD], gluten ataxia and dermatitis herpetiformis), allergic (wheat allergy) and idiopathic (non celiac gluten sensitivity, NCGS) [3,4]. In particular, Non-Celiac Gluten Sensitivity (NCGS) is a syndrome characterized by the onset of gastrointestinal and extraintestinal symptoms

after the ingestion of food containing gluten, and their regression after its withdrawal [5]. Although many points about NCGS need to be clarified, it seems frequent in the general population (at least 3%) and characterized by a clinical picture involving different extraintestinal symptoms, including those of neurological and psychiatric origin [6]. Based on these findings, different researchers are investigating the presence of biomarkers (antibodies against gluten and its fractions) in connection with adverse gluten reactions in patients affected by different disorders of unclear pathogenesis, such as Meniere's Disease (MD) [7]. MD is a clinical disorder defined as the idiopathic syndrome of endolymphatic hydrops [8]. Various causes have been ascribed, including trauma, viral infections, metabolic disorders, allergies, and autoimmune factors. MD is characterized by intermittent episodes of vertigo lasting from minutes to hours, with fluctuating sensorineural hearing loss, tinnitus, and aural pressure. MD is a disabling condition, owing to the recurrent vestibular symptoms, worsened by the progression of sensorineural hearing loss throughout its course. Although there is currently no cure, more than 85% of patients with Meniere's disease MD are helped by either changes in lifestyle (low sodium intake, dietary restriction) and medical treatment or by minimally invasive surgical procedures such as intratympanic steroid or gentamicin injections, and endolymphatic sac surgery [9,10]. We focused our study on the humoral immune responses to wheat antigens, particularly on the IgG and IgA antibody production against the repertoire of antigens and peptides associated with gliadin in patients with MD.

MATERIALS AND METHODS

Study design

Cross-sectional, case-control, observational study.

Patient selection

Twenty-eight MD patients (12 males, mean age 48.6 ± 7.1 years) and 16 females (mean age 49.3 ± 6.8 years), were enrolled. Following national and international guidelines, Celiac Disease (CD) and wheat allergies were excluded by means of negative anti tissue-transglutaminase IgA, low total IgA and sIgE dosage [4,11]. The MD patients were randomly extracted from the 5 years' follow-up population of a previous study from our group. [12] Only the patients with a diagnosis of "definite" MD have been included. According to the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) guidelines and to the criteria of the Barany Society [8], definite MD was diagnosed if there was a history of at least two spontaneous episodes of vertigo lasting 20 minutes to 12 hours; audiometrically documented low-to-medium frequency sensorineural hearing loss in 1 ear, of at least 30 dB, defining the affected ear on at least 1 occasion before, during, or after one of the episodes of vertigo; and fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear, not better accounted for by another vestibular diagnosis.

Briefly, the previous study showed that a high percentage of definite MD patients (82.7%) were positive to skin prick tests for one or more allergens; in particular, 75.76% of those who proved to be sensitive to gliadin, had a late-phase gliadin prick test response to the acid fraction of gluten (gliadin/glutentins), which is mainly caused by other immune mediators. The latter are released by IgE-dependent mast cell degranulation (slow reacting substances such as interleukin 5) rather than histamine, that is an immediately reacting substance [13].

Among the 28 unilateral MD patients, 14 were randomly selected from those reporting a symptomatic response while on a Gluten Free Diet (GFD) [MD/GS+] and 14 from those without response [MD/GS-]. At the time of serological tests, all the patients were on a gluten containing diet, all the MD/GS+ patients had absence of vertigo spells for more than six months, reduction of aural fullness and of gastrointestinal symptoms (dyspepsia, abdominal pain, and weight fluctuation). Patients with IgA deficiency were excluded from the study. All patients suffered of sporadic MD (not familial, group 1), they reported definite MD symptoms for at least 5 years. Comorbidities such as migraine and autoimmune, had been excluded. One hundred healthy subjects, matched for age and sex, (50 males and 50 females, mean age 46.8 ± 5.3 years) served as controls in order to establish the normal range of the tested biomarkers. In healthy controls, CD and wheat allergy were excluded as for MD patients.

Serological antibodies

An Enzyme-Linked Immunosorbent Assay (ELISA) IgG- IgM- and IgA-antibody testing against an array of wheat and associated antigens of both water-soluble and alcohol-soluble proteins

was carried out by Cyrex Laboratories (Phoenix, AZ, USA). The antibody panels that were run on every sample included:

1) the amount of IgA and IgG for the peptides (Wheat, Wheat Germ Agglutinin, Alpha Gliadin 33-mer, Alpha Gliadin 17-mer, Gamma Gliadin 15-mer, Omega Gliadin 17-mer, Glutenin 21-mer, Gluteomorphin/Dynorphin, Gliadin/Transglutaminase 2 Complex, Tg2 Tg3, Tg6)

2) the levels of IgG, IgM, IgA for Myelin Basic Protein, Cerebellar Peptide, Alpha and Beta Tubulin, Myelin Oligodendrocyte Glycoprotein, Ganglioside, Synapsin, Synaptophysin, Glutamic Acid Decarboxylase 65, Synapse Associated Protein) [14].

Statistical analysis

Levels of significance were calculated using the Statistical Package for the Social Sciences 19.0 for Windows (SPSS Inc, Chicago, IL). Owing to the small number of subjects in each group, the Mann–Whitney nonparametric test was used to compare groups (MD vs. controls). The antibody levels were expressed as total amount, means ± SD. Statistical analysis was also performed between age subgroups: MD/GS+ and MD/GS-. Exact Wilcoxon signed-ranks tests (2-tailed) were performed in order to analyse the differences between these two groups. A p_value < 0.05 was considered statistically significant.

Ethics

The participation in the study was voluntary and all the subjects were not paid for it. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation and with the Helsinki Declaration of 1964, as revised in 2008. This study was approved by the Ethical Committee of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy (19th July 2016). All participants provided a signed written consent to the study administrators. Participants' anonymity has been guaranteed.

RESULTS

The serological profiles of healthy subject and in MD patients are reported in (Table 1). In general, a slight increase of titers against almost all the analyzed biomarkers was observed. However, the increase was statistically significant only for anti-wheat IgA, anti-cerebellar peptide IgA and anti- glutamic acid decarboxylase (GAD) 65 IgM.

In (Table 2), a comparison between the serological profiles of MD/GS+ and MD/GS- groups is reported. An increased titer of anti-wheat IgA was confirmed in MD/GS+ compared to MD/GS- (0.7 ± 0.5 vs 0,4 ± 0.2, p=0.034. The normal range in healthy subjects was 0.3 ± 0.17.

A significant increase of GAD IgM associated with a reduction of GAD IgG was observed in MD/GS+ patients compared to the MD/GS- (0.79 ± 0.7 vs 0.37 ± 0.3 p=0.049; 0.51 ± 0.31 vs 0.97 ± 0.50, p=0.001, respectively).

A reduction of the anti-transglutaminase 3 IgG (p=0.001), anti-myelin basic protein IgG (p=0.039) and anti-myelin oligodendrocyte glycoprotein IgG (p=0.01) was also noted in MD/GS+ patients compared to MD/GS-. These variations occurred within the normal ranges and should be considered with caution, in particular when not associated with a concomitant significant modification of the IgM or IgG or IgA titers against the same antigens.

DISCUSSION

Many authors are studying the characterization of the whole repertoire of wheat antigens involved in the humoral immune responses in patients with wheat-related diseases, in order to define the possible overlap of NCGS with other inflammatory bowel diseases and extraintestinal disorders targeting the nervous system [7,14]. In such cases, the innate or adaptive immune response (humoral or cellular) to gluten/wheat results in the presentation of three distinct conditions that are triggered by the ingestion of wheat protein: CD, wheat allergy, and NCGS [15,16]. A possible relationship between NCGS and MD has been previously suggested [12,17].

Early studies categorized wheat proteins into four groups according to solubility: water-soluble albumins, salt-soluble globulins, ethanol-soluble gliadins, and alkaline/acid-soluble glutenins [18]; however, the proteomic map of wheat identified ~ 1000 individual antigens [19]. For this specific reason, we planned to check the serological profile, in search of a possible useful biomarker to assist in diagnosing the sensitivity and the immune reactivity to gluten.

Anti-wheat IgA, that resulted increased in MD group compared to the controls, is an expression of the increased mucosal response to a poliantigenic extract (Triticum aestivum) containing gliadin, gluten and other peptides, in the MD subjects. Anti-wheat IgA increase was also confirmed in the

MD/GS+ group (GFD responsive) compared to the MD/GS- group (GFD unresponsive). This finding supports the hypothesis of a relation between the intake of food containing wheat/gluten and MD. In a recent work, an altered intestinal permeability has been documented in active MD subjects [20]. Considering that IgA have a mucosal origin and are mainly produced by the small bowel, the existence of a gut-brain immunological axis is highly likely [21]. However, anti-wheat IgA are found in high rates also in normal blood donors [21] and in 33% of asthma bakery subjects [22]; therefore these results should be considered with caution.

Table 1: Antibodies to the repertoire of wheat antigens in MD and controls.

Biomarker	controls	MD	p_value	Biomarker	controls	MD	p_value
Wheat IgG	0.9 +/- 0.3	1.00 +/- 0.47	n.s.	Myelin Basic Protein IgA	0.56 +/- 0.23	0.84 +/- 0.59	n.s.
Wheat IgA	**0.3 +/- 0.17**	**0.72 +/- 0.51**	**<0.05**	Cerebellar Peptide IgG	0.47 +/- 0.23	0,63+/- 0.27	n.s.
Wheat Germ Agglutinin IgG	0.8 +/- 0.24	0.87 +/- 0.46	n.s.	Cerebellar Peptide IgM	0.56 +/- 0.29	0.59 +/- 0.39	n.s.
Wheat Germ Agglutinin IgA	0.35 +/- 0.21	0.41 +/- 0.20	n.s.	**Cerebellar Peptide IgA**	**0.48 +/- 0.24**	**0,81 +/- 0.60**	**<0.05**
Alpha Gliadin 33-mer IgG	0.6 +/- 0.28	0.84 +/- 0.64	n.s.	Alpha and Beta Tubulin IgG	0.7 +/- 0.32	0.62 +/- 0.63	n.s.
Alpha Gliadin 33-mer IgA	0.2 +/- 0.14	0.19 +/- 0.19	n.s.	Alpha and Beta Tubulin IgM	0.51 +/- 0.23	0.56 +/- 0.51	n.s.
Alpha Gliadin 17-mer IgG	0.3 +/- 0.15	0.30+/- 0.17	n.s.	Alpha and Beta Tubulin IA	0.31 +/- 0.13	0.41 +/- 0.23	n.s.
Alpha Gliadin 17-mer IgA	0.21 +/- 0.13	0.22+/- 0.28	n.s.	Myelin Oligodendrocyte Glycoprotein IgG	0.6 +/- 0.26	0.74 +/- 0.37	n.s.
Gamma Gliadin 15-mer IgG	0.69 +/- 0.26	0.94+/- 0.66	n.s.	Myelin Oligodendrocyte Glycoprotein IgM	0.53 +/- 0.24	0.81 +/- 0.58	n.s.
Gamma Gliadin 15-mer IgA	0.22 +/- 0.13	0.31+/- 0.21	n.s.	Myelin Oligodendrocyte Glycoprotein IgA	0.54 +/- 0.27	0.77 +/- 0.34	n.s.
Omega Gliadin 17-mer IgG	0.47 +/- 0.23	0.42 +/- 0.30	n.s.	Ganglioside IgG	0.38 +/- 0.25	0.66 +/- 0.43	n.s.
Omega Gliadin 17-mer IgA	0.25 +/- 0.16	0.35 +/- 0.28	n.s.	Ganglioside IgM	0.66 +/- 0.35	0.94 +/- 0.66	n.s.
Glutenin 21-mer IgG	0.9 +/- 0.33	1,13+/- 0.82	n.s.	Ganglioside IgA	0.47 +/- 0.21	0.66 +/- 0.38	n.s.
Glutenin 21-mer IgA	0.38 +/- 0.24	0.46 +/- 0.27	n.s.	Glutamic Acid Decarboxylase 65 (GAD 65) IgG	0.81 +/- 0.29	0.58 +/- 0.36	n.s.
Gluteomorphin/Dynorphin IgG	0.43 +/- 0.19	0.41 +/- 0.30	n.s.	**Glutamic Acid Decarboxylase 65 (GAD 65) IgM**	**0.41 +/- 0.18**	**0.74 +/- 0.68**	**<0.05**
Gluteomorphin/Dynorphin IgA	0.21 +/- 0.11	0.22 +/- 0.16	n.s.	Glutamic Acid Decarboxylase 65 (GAD 65) IgA	0.5 +/- 0.17	0.49 +/- 0.18	n.s.
Gliadin/Transglutaminase 2 Complex IgG	0.51 +/- 0.23	0.60 +/- 0.46	n.s.	Synapsin IgG	0.17 +/- 0.13	0.23 +/- 0.31	n.s.
Gliadin/Transglutaminase 2 Complex IgA	0.15 +/- 0.9	0.23 +/- 0.17	n.s.	Synapsin IgM	0.38 +/- 0.17	0.62 +/- 0.59	n.s.
Transglutaminase 2 IgG	1.1 +/- 4.3	1.15 +/- 0,51	n.s.	Synapsin IgA	0.17 +/- 0.12	0.24 +/- 0.20	n.s.
Transglutaminase 2 IgA	0.4 +/- 0.24	0,70 +/- 0.41	n.s.	Synaptophysin IgG	0.54 +/- 0.21	0.55 +/- 0.48	n.s.
Transglutaminase 3 IgG	0.52 +/- 0.27	0.55 +/- 0.27	n.s.	Synaptophysin IgM	0.48 +/- 0.19	0.60 +/- 0.53	n.s.
Transglutaminase 3 IgA	0.23 +/- 0.18	0.33 +/- 0.20	n.s.	Synaptophysin IgA	0.32 +/- 0.17	0.37 +/- 0.23	n.s.
Transglutaminase 6 IgG	0.43 +/- 0.22	0.49 +/- 0.30	n.s.	Synapse Associated Protein IgG	0.42 +/- 0.18	0.55 +/- 0.42	n.s.
Transglutaminase 6 IgA	0.21 +/- 0.15	0.25 +/- 0.12	n.s.	Synapse Associated Protein IgM	0.47 +/- 0.21	0.88 +/- 0.69	n.s.
Myelin Basic Protein IgG	0.6 +/- 0.21	0.71 +/- 0.31	n.s.	Synapse Associated Protein IgA	0.3 +/- 0.17	0.28 +/- 0.15	n.s.
Myelin Basic Protein IgM	0.54 +/- 0.19	0.69 +/- 0.35	n.s.				

Table 2. Gluten biomarkers in MD-GS+ and MD-GS- subjects.

Biomarker	controls	MD	MD-GS-	MD-GS+	p_value
Wheat IgG	0.9 +/- 0.3	1.00 +/- 0.47	1.0 +/- 0.50	1.1 +/- 0.50	n.s.
*** Wheat IgA**	**0.3 +/- 0.17**	**0.72 +/- 0.51**	**0.41 +/- 0.21**	**0.74 +/-0.50**	**0.034**
Transglutaminase 3 IgG	0.52 +/- 0.27	0.55 +/- 0.27	**0.86 +/- 0.38**	**0.52 +/- 0.24**	**0.001**
Transglutaminase 3 IgA	0.23 +/- 0.18	0.33 +/- 0.20	0.36 +/- 0.25	0.33 +/- 0.20	n.s.
Cerebellar Peptide IgG	0.47 +/- 0.23	0,63+/- 0.27	0.64 +/- 0.21	0.63 +/- 0.27	n.s.
Cerebellar Peptide IgM	0.56 +/- 0.29	0.59 +/- 0.39	0.51 +/- 0.28	0.83 +/- 0.60	n.s.
*** Cerebellar Peptide IgA**	**0.48 +/- 0.24**	**0,81 +/- 0.60**	0.52 +/- 0.22	0.60 +/- 0.40	n.s.
Myelin Basic Protein IgG	0.6 +/- 0.21	0.71 +/- 0.31	**0.90 +/- 0.27**	**0.69 +/- 0.31**	**0.039**
Myelin Basic Protein IgM	0.54 +/- 0.19	0.69 +/- 0.35	0.76 +/- 0.71	0.87 +/- 0.59	n.s.
Myelin Basic Protein IgA	0.56 +/- 0.23	0.84 +/- 0.59	0.85 +/- 0.40	0.70 +/- 0.35	n.s.
Myelin Oligodendrocyte Glycoprotein IgG	0.6 +/- 0.26	0.74 +/- 0.37	**1.04 +/- 0.44**	**0.71 +/- 0.35**	**0.013**
Myelin Oligodendrocyte Glycoprotein IgM	0.53 +/- 0.24	0.81 +/- 0.58	0.86 +/- 0.79	0.83 +/- 0.58	n.s.
Myelin Oligodendrocyte Glycoprotein IgA	0.54 +/- 0.27	0.77 +/- 0.34	0.79 +/- 0.38	0.77 +/- 0.35	n.s.
Glutamic Acid Decarboxylase 65 (GAD 65) IgG	0.81 +/- 0.29	0.58 +/- 0.36	**0.97 +/- 0.50**	**0.51 +/- 0.32**	**0.001**
*** Glutamic Acid Decarboxylase 65 (GAD 65) IgM**	**0.41 +/- 0.18**	**0.74 +/- 0.68**	**0.37 +/- 0.31**	**0.79 +/- 0.72**	**0.049**
Glutamic Acid Decarboxylase 65 (GAD 65) IgA	0.50 +/- 0.17	0.49 +/- 0.18	0.43 +/- 0.13	0.51 +/- 0.21	n.s.

*the difference between MD and controls was statistically significant.

On the other hand, in our study the transglutaminases do not seem to be involved as autoantigens, in contrast to what is observed in the "classical" gluten-related autoimmune pathway. The transglutaminase enzymatic family is usually targeted in the GRD with an autoimmune mechanism: transglutaminase type 2 in CD, transglutaminase type 6 in neurological diseases and type 3 in dermatitis herpetiformis [4]. In our cohort of MD patients, we did not notice any sign of anti-transglutaminase reaction. The increase of anti-cerebellar peptide IgA was an isolated finding; instead, a significant increase of GAD IgM associated with a reduction of GAD IgG was observed in MD patients and further confirmed in MD/GS+ patients compared to the MD/GS-. Anti-GAD antibodies are particularly common in autoimmune diseases, such as thyroid disease and rheumatoid arthritis. There are two isoenzymes of GAD, with molecular weights of 67 and 65 kDa, respectively [23].

In the literature, higher titers of Ab anti GAD 65 (>1.53) are used in the differential diagnosis between a late onset of type 1 and type 2 diabetes mellitus [23]. Antibodies against GAD 67 have been linked with a disease characterized by stiffness of the muscles, acute vestibular damage and cerebellar ataxia, possibly related to a lack of gamma aminobutyric acid [24]. No other reports on acute vestibular damage and anti-glutamic acid decarboxylase antibodies have been described so far. Our findings of an increase of anti-GAD 65 IgM in the MD group supports the possible role of gamma aminobutyric acid as a neurotransmitter in the peripheral vestibular system [24] Finally, it is well known that the incidence of autoimmune diseases and thyroiditis is increased in a similar fashion in MD [8,25] and in NCGS [26]. Unfortunately, in these patients, anti-thyroid antibodies have not been tested.

CONCLUSIONS

In the present study we observed a slightly different serological profile in definite MD patients responding and not responding to a GFD, with the concomitant presence of an immunological reaction against gluten and autoimmune antigens of the nervous system. Unfortunately, none of the studied biomarkers resulted disease-specific; thus, the humoral response to wheat is insufficient, per se, in order to certainly identify the association between GRD and MD. This association

still needs to be supported by dietary exclusions and challenges: symptoms improve or disappear upon gluten withdrawal, while they recur if gluten is reintroduced in the diet[27]. However, withdrawal diets and subsequent challenge tests are frequently declined by patients, owing to the consistent side effects. For this reason, further studies are required to define the clinical relevance of other biomarkers.

ACKNOWLEDGMENTS

The Authors are grateful to Dr. O'Bryan and to the Cyrex Laboratories for the serological analysis; to Dr Luigi Di Berardino for his immunological expertise and advice.

No funding source was secured for this study. The authors report no financial interest in the subject matter, no actual/potential conflict of interest. Authors have no relationship with commercial companies.

AUTHOR CONTRIBUTIONS

This paper has not been published elsewhere and has not been submitted simultaneously for publication elsewhere.

FDB conceived and designed the study, has followed directly the patients, wrote the paper.

DZ analyzed data, wrote, supervised and reviewed the article.

LE gave his technical and specialist support; analyzed data; reviewed the article.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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