

Gluten Sensitivity in Meniere's Disease

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Objectives/Hypothesis: Wheat is one of the most common food allergens found in patients with Meniere's disease (MD). Gluten from wheat has been identified to have a etiopathogenetic role in celiac disease, IgE hypersensitivity to wheat disease, and recently to gluten sensitivity. The aim of this study was to verify the incidence of gliadin prick test response in patients affected by MD.

Study Design: Prospective individual case-control study.

Methods: There were 58 adult patients with definite MD, 25 healthy volunteers, and 25 patients with grass pollen rhinoconjunctivitis tested with skin prick test to gliadin.

Results: A total of 33 MD patients (56.9%) proved to be sensitive to gliadin, eight of whom were positive to prick test after 20 minutes, 13 after 6 hours, 11 after 12 hours, and one after 24 hours.

Conclusions: This is the first report of gliadin skin test response in MD. Further studies are needed to define the relationship between immune response to wheat proteins and MD symptoms.

Key Words: Meniere's disease, gluten sensitivity, wheat, gliadin, food allergy.

Level of Evidence: 3b.

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INTRODUCTION

Meniere's disease (MD) is a clinical disorder defined as the idiopathic syndrome of endolymphatic hydrops. Various causes have been ascribed, including trauma, viral infections, metabolic disorders, allergies, and autoimmune factors.

Since 1923, inhalant and food allergies have been linked with MD symptoms,¹ and many studies have addressed the difficulties in confirming a relationship between allergy and MD.² In our previous review,³ we concluded that the relationship between two multifactorial diseases is very difficult to establish, particularly when the causative effect is not necessarily immediate. Moreover, although it is also known that the majority of allergic diseases occur during childhood, only approximately 3% of all MD patients are in the pediatric age group.

It is well known that an appropriate elimination diet for documented food allergies can prevent an immune-mediated reaction, and earlier published treatment results have shown benefit from dietary restriction for symptoms of MD in patients with both allergy and MD.⁴ However, the weakness of these results is that there were no control groups receiving given diets eliminating foods that were negative on testing.²

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Since 2000, it has been reported that wheat is the most common food allergen found in patients with MD (68.2%).⁵ It is also known that in subjects suffering from wheat allergy, gliadin is the major cause of IgE-mediated hypersensitivity.⁶ For this reason, we decided to add wheat gliadin to our standard prick tests for MD patients. The aim of this study was to verify the incidence of gliadin IgE hypersensitivity in patients affected by MD.

MATERIALS AND METHODS

From July 2010 to December 2010, a total of 58 patients between ages of 35 and 66 years diagnosed with definite MD were recruited to this study. Definite MD diagnosis was carried out according to the American Academy of Otolaryngology–Head and Neck Surgery Committee on Hearing and Equilibrium (AAO-HNS CHE) criteria.⁷ All patients had a history of at least two definitive spontaneous episodes of vertigo lasting 20 minutes or longer, tinnitus, or aural fullness, and audiometrically documented sensorineural hearing loss of at least 60 dB on at least one occasion, whereas other pathologies and acute forms were excluded. Peripheral vestibular lesions were defined by canal paresis calculated using Jongkees' formula and superior to 25% at the bithermal caloric test according to the Hallpike technique.

Furthermore, an inclusion criteria was the absence of any pharmacological treatment during the observational period. Exclusion criteria were also previous or concurrent therapy with corticosteroids and/or antihistamines within the last month. Exclusion criteria also included seropositivity for antendomysium antibodies IgA and antitransglutaminase IgA, and high serum total and/or wheat-specific IgE. Subjects with type 1 diabetes, inflammatory bowel disease, *Helicobacter pylori* infection, and parasitosis were also excluded because these conditions give rise to altered intestinal permeability.

The control groups consisted of 25 healthy volunteers and 25 multiply sensitized (more than three positive allergens at skin prick testing) patients with grass pollen rhinoconjunctivitis

TABLE I.
Number of Meniere's Disease Patients With Positive
Skin Prick Tests.

	Monosensitized	Polysensitized		
		Plus Inhalant	Plus Other Fresh Food	Plus Inhalant and Other Fresh Food
Gliadin	20	3	2	8
Tomato	2	2	1	2
Inhalant	8	0	0	0

who were from the same age group and lived in the same region. Subjects were tested with our standard battery of skin tests using a standard method: 1) prick tests for the most common inhalants, cow milk proteins, ovalbumin, and water extract from wheat flour; and 2) prick tests with tomato, potato, apple, and carrot (fresh food). In addition, the prick test for gliadin was carried out using 125 µg/mL wheat gliadin in 50% hydroglyceric extract. Histamine was used as a positive control and extract diluent as a negative control.

Reactions were recorded 20 minutes after testing. The results were expressed as the percentage of the mean wheal diameter provoked by the allergen compared with that provoked by histamine. Skin prick tests were positive if the percentage of the mean wheal diameter provoked by the allergen compared with that provoked by histamine was higher than 50% with at least 3 mm of mean wheal diameter. Because many patients reported a late-phase response, we also recorded the positive response after 6 to 12 and 24 hours.

RESULTS

A total of 48 MD patients (82.7%) were positive to skin prick tests for one or more allergens. There were 33 patients who proved to be sensitive to gliadin, and 20 of those patients were monosensitized and 13 showed a positive prick test to other allergens (Table I). Only 8/33 MD patients were positive to gliadin prick test at 20 minutes. The other 25 showed a late response reaction; 13 were positive at 6 hours, 11 at 12 hours, and one at 24 hours. No MD patients were positive to wheat flour water extract. The prick test for gliadin was negative in all healthy volunteers and in all patients with grass pollen rhinoconjunctivitis.

DISCUSSION

The gliadins are a family of glutamine- and proline-rich monomeric proteins that account for 40% to 50% of the total protein content of wheat kernels. The alcohol-soluble gliadins aggregate with the alcohol-insoluble glutenins to form gluten, which is responsible for the structure and properties of wheat dough. It is known that gliadins are responsible for inducing IgE hypersensitive disease (immediate response). However, we were surprised to find that many patients had a late-phase response to gliadin. Late-phase response occurring 6 to 12 hours after skin prick testing is described in the literature, in particular in atopic disease subjects, and is blocked by glucocorticosteroids.^{8,9} It is mainly caused by other immune mediators (slow reacting substances such as inter-

leukin 5) rather than histamine (immediately reacting substance), which are in any case released by IgE-dependent mast cell degranulation.¹⁰ A late phase response to a food allergen prick test has already been reported in atopic children,¹¹ and Meding et al. reported a late phase skin prick test reaction to malted wheat in seven bakers affected by hand eczema.¹² In this last work, the authors immunohistochemically analyzed the reaction observed and found a mild to moderate perivascular dermal cell infiltrate consisting mainly of CD4 and HLA- DR+ cells.

Research carried out by Kiecolt-Glaser et al.¹³ suggests that late phase skin prick test responses in allergic patients are substantially enhanced by stress and anxiety, which are associated with an increase of interleukin 6. The authors of this study conclude that stress and anxiety can be responsible for worsening and prolonging the symptoms of allergic rhinitis. In accordance with this observation, we found a higher prevalence of late phase responses to gliadin in MD patients who are notably prone to anxiety and stress.¹⁴⁻¹⁷ Furthermore, the effect of stress on MD is not a psychological byproduct, but it does contribute to inner ear pathology and is a trigger of MD attacks.¹⁶

What is to be inferred by the fact that 33 (56.9 %) patients with MD proved to be skin prick test positive to gliadin? A positive skin prick test to a food allergen is not considered proof of allergy, and may represent sensitization without clinical manifestations.¹⁸ Furthermore, recent articles have highlighted the fact that, besides celiac disease and wheat allergy, there are also cases of gluten reactions, generally defined as gluten sensitivity (GS), in which neither allergic nor autoimmune mechanisms are involved.¹⁹ GS is a condition associated with prevalent gluten-induced activation of innate, rather than adaptive immune responses in the absence of detectable changes in mucosal barrier function.²⁰

The overall clinical picture of GS is generally less severe than celiac disease and is not accompanied by the concurrence of tissue transglutaminase autoantibodies or autoimmune comorbidities. In fact, GS and celiac disease are two different clinical entities.²¹ Furthermore, the extraintestinal symptoms of GS differ from those of celiac disease and include bone or joint pain osteoporosis, leg numbness, muscle cramps, unexplained anemia, glossitis, and thyroiditis. Thyroiditis and leg numbness are also frequently reported by MD patients.

In clinical practice, it is well known that MD patients frequently complain of symptom-complex of the aspecific gastrointestinal tract, such as diarrhea, abdominal pain, dyspepsia, and weight fluctuation; however, this observation is hidden by the importance of otological manifestations (hypacusis and vertigo).²² The observation of late skin reactions to gliadin suggests that further investigation into the response to the other wheat protein fractions is necessary to define skin responses better from an immunohistochemical point of view. However, this is not easy because there are no standardized prick test extracts commercially available.

Typically, the diagnosis of GS is made by exclusion, and an elimination diet and open challenge (i.e., the monitored reintroduction of gluten-containing foods) are

most often used to evaluate whether the patient's health improves with the elimination or reduction of gluten from the diet. For a precise diagnosis, double-blind placebo-controlled food challenge is necessary, but this is difficult to perform in MD patients. Furthermore, the AAO-HNS CHE criteria for MD therapy evaluation, mandatory for the appraisal of the results,²³ do not give any referring criteria for this approach. In any case, response to treatment by means of elimination of food allergens must be assessed to define the relation between food hypersensitivity and MD symptoms. The problem is how long the modified diet must last to eliminate the MD symptoms effectively.

CONCLUSION

As far as we know, this is the first report of late gliadin prick test response in MD. Further studies are needed to define the relation between GS and MD symptoms to evaluate whether it is casual or has a causative role in MD.

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