



## Delayed immunomodulatory effect of cow-milk free diet in Meniere's Disease.

Journal:	<i>Journal of the American College of Nutrition</i>
Manuscript ID	UACN-2017-0050.R1
Manuscript Type:	Report
Date Submitted by the Author:	n/a
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Keywords:	food allergy, Ménière Disease, elimination diet, challenge, cow-milk proteins, immunotherapy, mites, grass
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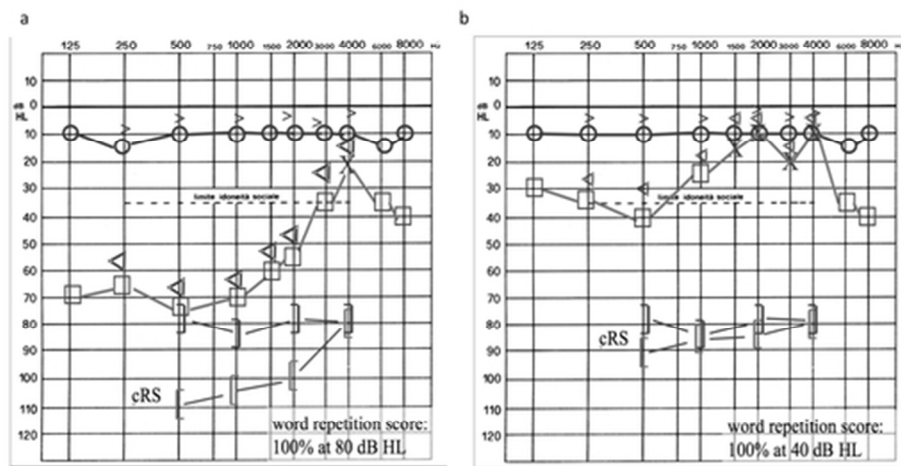


Figure 1

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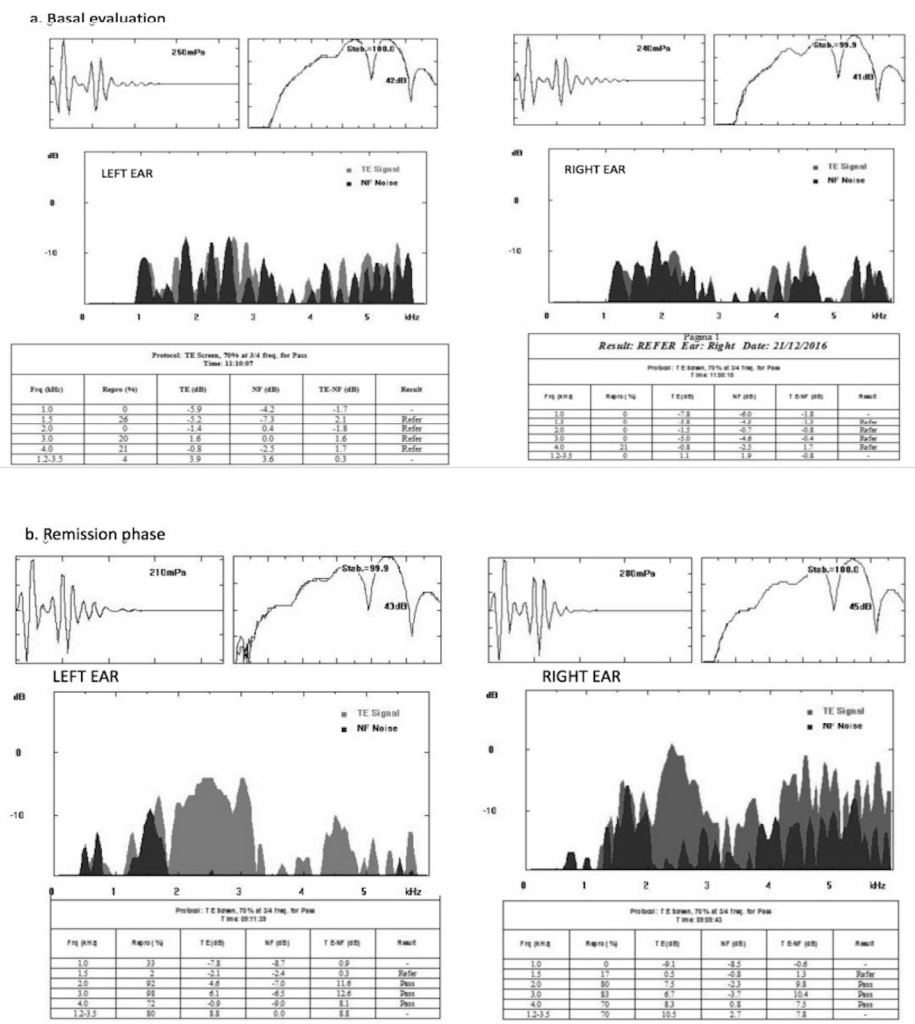


Figure 2

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## Delayed immunomodulatory effect of cow-milk free diet in Meniere's Disease

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**Key-words:** Ménière Disease; food allergy; immunotherapy; elimination diet; mites; grass; cow-milk proteins; atopy, challenge.

**Running title:** The effect of cow-milk free diet in Meniere's Disease

**Ethical Standards.** This case report has been approved by the Ethical Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy (*IRB n. 1025 – 12/5/2015*). The patient has signed written consent for publication.

**Conflicts of Interest and Source of Funding.** This work has not been published elsewhere and has not been submitted simultaneously of publication elsewhere. This case-report has not been presented at any meeting. The Author has no relationship with commercial companies. No external funding sources supported this research. The Authors reports no conflict of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. **Acknowledgements:** The Authors are grateful to Prof Cesarani and Dr Luigi Di Bernardino for his precious comments and clinical experience.

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**Abstract**

**Objective.** Since 1930, dietary modification has been proposed as adjunct treatment in Ménière's disease (MD) with different and controversial results. The Authors reported the case of a 42-year-old female suffering from definite MD and intermittent seasonal allergic rhino-conjunctivitis because it highlights the importance of evaluating the different combinations of defined causative elements in an atopic patient with MD. **Methods.** An immunological and audiological evaluation has been performed, including pure-tone, speech and immittance audiometry, glycerol dehydration test, bithermal caloric testing, video-head impulse test, cervical vestibular evoked myogenic potentials, static posturography and Dizziness Handicap Inventory questionnaire. **Results.** Milk-free diet was crucial to the relief from MD symptoms and the cow's milk challenge test was able to evoke them but vestibular symptoms persists. **Conclusions.** The effect of dietary modification was evident only after specific immunotherapies against other allergens. This highlights the importance of evaluating different combinations of defined causative elements also in the allergic treatment of MD.

## Introduction

Since 1930, low salt diet has been proposed to treat Ménière's disease (MD) patients [1] and inhalant and food allergies have been linked with MD symptoms. [2] In 1972, Bryan & Bryan first reported a benefit in MD patients following an elimination diet for documented food allergies. [3] In 2000, Derebery claimed that the prevalence of allergy in patients with MD is almost three times that of the general population. [4] The immunological facets of allergy and their relationship with MD has been explained in different ways. [5] Among the most common food allergens, the role of wheat and milk in MD has been hypothesized. [5, 6, 7] Animal studies have shown evidence of immunologic activity within the inner ear in MD. [8]

In a recent review by Weinreich and Agrawal, [9] a possible association between allergy and MD has been observed in a number of cross-sectional and observational studies, suggesting the need for inclusion of allergy control in the treatment plan for bilateral MD, or in case of development of symptoms within a short time after exposure to food or inhaled allergens. However, in multifactorial conditions, such as in MD, and in immune mediated diseases, the effect of causative therapies on symptoms might not be immediately detected. [10]

We add to this unresolved issue a personal observation on a MD patient in whom only a combination of a specific diet and immunotherapies was able to relieve the patient from her symptoms.

### Case history

We describe the case of a 42-year-old female affected, since 2009, by “definite” MD in her left ear, according to the criteria of the American Academy of Otolaryngology-Head and Neck Surgery Committee on Hearing and Equilibrium (AAOHNS-CHE). [10]

She started complaining of tinnitus in 2001 (Tinnitus Handicap Inventory [THI]: 42/100); vertigo and aural fullness began in 2008 with recurrent episodes (more than 4 episode/month) of audiometrically documented sensorineural hearing loss of at least 60 dB HL in the left ear; word repetition score was 100% at 80 dB HL during the acute stage. (Figure 1). During vertigo spells, the patient also experienced hearing loss, tinnitus, and aural pressure; all symptoms would disappear after a few hours of bed rest. Glycerol dehydration test showed an improvement of 20 dB HL at the pure-tone threshold at 250-500 Hz in the acute phase. A left peripheral vestibular weakness was detected by bithermal caloric testing according to the Hallpike technique and Jongkee’s formulae); the head impulse vestibulo-ocular reflex gain was decreased on the left side, by video-head impulse test (vHIT). Since the initial diagnosis of MD, she had been treated with a low-sodium diet, diuretics, and steroids, but none of the symptoms had improved. In the critical phase, the cervical vestibular evoked myogenic potentials (cVEMP) revealed a bilateral absence of p13-n23 complex; transiently evoked otoacoustic emission (TEOAE) were bilaterally absent (Figure 2) and the functional stabilometric parameters (SVEP system 6.0, Amplaid, Politecnica Modena, Italy) were persistently abnormal during critical and intercritical phases. From 2008 to 2013, more than 4 episode/month occurred repeatedly, while the symptoms-free intervals lasted no more than 6 weeks. The vertigo spells were more frequent in February, March, May, June and November.

During those months, the presence of aeroallergens (count per cubic meter) that were regularly monitored throughout the year by checking the bulletin obtained from the local Pollen Count Station [11], reached their concentration peaks.



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3 Disability was evaluated by the Dizziness Handicap Inventory (DHI: 56/100, physical 14,  
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5 emotional 18 and functional 24).  
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8 The patient had suffered from intermittent and seasonal allergic rhino-conjunctivitis since  
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10 1985. In 2012, skin tests were carried out in accordance with the recommendations of the  
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12 European Academy of Allergology and Clinical Immunology [12]: prick tests were positive  
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14 to house dust mite, grass and birch pollen, and cow milk proteins, while they were negative to  
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16 the other most common inhalant and fresh food allergens and to gliadin, even after 24 hours.  
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18 Specific IgE to Dermatophagoides mix, grass pollen, betulaceae and milk were in class 3 - 4  
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20 (RAST-CAP System EIA method, Pharmacia, Uppsala, Sweden.). The common  
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22 autoantibodies profile was negative. A possible role of allergy in the symptoms of MD was  
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24 suspected and, in October 2012, the patient initially tried a deprivation diet, eliminating foods  
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26 that contain cow milk and its derivatives. **The patient was allowed to consume only soy and**  
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28 **rice milk, while other milk products, such as sheep or goat milk/cheese were avoided,** but  
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30 symptoms persisted for the following six months. No other pharmacological treatment was  
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32 administered during and after the dietary period. In March 2013, the patient began two  
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34 concurrent subcutaneous immunotherapies (SARM allergeni, Guidonia-Rome, Italy) one for  
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36 mites (40% Dermatophagoides, 30% Gliciphagidae and 30% Acaridae) and another one for  
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38 grass pollen (80% mix: Dactylis, Festuca, Lolium, Phleum, Poa, Agrostis, Antoxanthum and  
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40 20% Cynodon D).  
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46 The remission of the majority of MD symptoms (excluding tinnitus) was achieved during the  
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48 first three months after treatment. Pure tone threshold audiometry showed a steady gain of air-  
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50 conducted hearing threshold up to 30 dB HL at 500-1000-2000 Hz; word recognition score  
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52 reached 100% at 40 dB HL; (Figure 1) similarly, over the same period the allergic symptoms  
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54 progressively decreased in a significant manner. The stabilometric parameters returned to  
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56 normal values and TEOAE were elicited in more than two occasions. (Figure 2) On the other  
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3 hand, a persistence of the left peripheral vestibular weakness was detected upon bithermal  
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5 caloric testing and vHIT. while, during the remission phase, c-VEMPS were not retested.  
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9 The benefits persisted for one year during the exclusion diet, until the patient agreed to  
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11 undergo an open challenge; in February 2014, cow milk and its derivatives were reintroduced  
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13 in her diet; this challenge procedure is considered the reference gold standard for the  
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15 diagnosis of cow's milk proteins allergy according to the diagnostic recommendations  
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17 guidelines. [12] This provocation test caused an acute episode with an audiometrically  
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19 documented sensorineural hearing loss of 60 dB HL in the left ear, disappearing of TEOAE  
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21 and the reactivation of MD symptoms, occurring 6 hours after the ingestion. The symptoms  
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23 subsided after two days when milk was once again removed from the diet. The benefits of  
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25 immunotherapy on MD symptoms still persist 2 years and a half after the milk challenge test.  
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27 Up to date, the patient is still free from vertigo and hearing fluctuations; she is only  
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29 complaining of a mild tinnitus (THI 12/100). DHI has greatly improved to 8/100 (physical 0,  
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31 emotional 2 and functional 6).  
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36 The comparison between the frequency of MD attacks during the 6 months prior to the  
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38 immunomodulation treatment and the 18 to 24 months period after treatment, according to the  
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40 AAO-CHE guidelines, showed a "complete" control of definite spells (class A). (Table 1)  
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## Discussion

MD, likewise atopy, is a multifactorial condition. [13] Possible correlations between multifactorial diseases are very difficult to establish, particularly when the causative effect is not immediate; large cohorts of homogeneous patients need to be recruited for conducting randomized clinical studies and this explains the still incompletely proven relationship between the two conditions; in this respect clinical case reports acquire relevance. In a previous study from our group, [7] sensitivity to gluten was found to be associated with MD and the incidence of atopy was confirmed to be high in MD subjects. In 2000, Derebery first reported data from a mail-posted survey showing overall decrease of MD and allergy symptoms secondary to anti-allergic treatment. [5] The same author concluded that it is logical to assume that down-regulating the production and release of pro-inflammatory and vasoactive mediators that promote fluid extravasation and/or retention could help lessen the symptoms of MD. The ingestion of causative allergens also might induce an altered gastroenteric permeability in patients with hypersensitivity; [14] it is not known if this condition can induce a variation in the electrolytic balance.

The patient's increase of vertigo spells in February, March, May, June and November paralleled the raised inhalant allergen concentrations. Based on the local Pollen Count by the European approved monitoring station [11], in the patient's environment the Betulaceae reached their peaks in February and March and grass pollen in May and June. Furthermore, in November, an increase of dust mites is commonly reported, due to the house heating onset and the subsequent rise of room temperatures. [15, 16]

Antigens avoidance and specific immunotherapy (SIT) are the only accepted treatments that can favourably change the natural history of allergic disease, because they are reconditioning the immune system to a specific level of tolerance towards the allergens (a.k.a.

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3 immunomodulation). [17] However, even if an international consensus has been reached in  
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5 2015 [17] about immunomodulation of allergic patients with SIT, its role in MD patients is  
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7 still unclear. [9] In our patient, the target of SIT was to induce the specific hypo-sensitization  
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9 to aeroallergens; besides that, it helped us finding the concomitant hyper-sensitization to  
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11 cow's milk. The causative components of milk allergy, according to the World Allergy  
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13 Organization (WAO) Special Committee on Food Allergy guidelines, are supposed to be the  
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15 cow milk proteins [18]  
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19 On the other hand, the patient did not show any allergic reaction to the oral intake of  
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21 foods which are cross-reacting with aeroallergens (apple, pear, halzelnut, carrots, selery and  
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23 fennel with Betulaceae, tomato with grass pollen and shrimps with mites), thus showing a  
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25 different organ target tropism. [19]  
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28 SIT has a profound immune-regulatory effect that may also explain why it can modify  
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30 the course of allergic disease with a long-lasting effect even after discontinuation of  
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32 treatment. However, SIT is a highly allergen-specific form of treatment, targeting only the  
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34 allergens included in the vaccine; for this reason, other cross-reactive or non-immunologically  
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36 related allergens responsible of immune inflammation remain untreated. [20] This combined  
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38 effect of food and inhalant allergies is particularly noteworthy: immunomodulation induced  
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40 by the elimination diet was not sufficient to treat our patient; only the more consistent  
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42 immunomodulation prompted by the combined SIT was able to relieve her MD symptoms.  
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48 Similarly to the other immune-mediated disorders, allergy is likely to produce a bilateral  
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50 involvement of the ear. In the literature, a bilateral simultaneous onset of MD has been  
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52 observed in 11% of the cases; however, the rate of delayed progression from unilateral to  
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54 bilateral involvement is relevant; it requires long-term follow-up for identification (on  
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56 average:  $7.6 \pm 7.0$  years) and might be conditioned by pharmacological therapies [21]. Even if  
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3 the majority of MD have a unilateral onset, some of the audio-vestibular tests may already  
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5 suggest the involvement of the contralateral ear. Recent studies using 3-dimensional fluid-  
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7 attenuated inversion recovery magnetic resonance imaging showed endolymphatic hydrops in  
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9 the asymptomatic contralateral ear in long-standing MD patients, in support of this  
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11 hypothesis. [22]  
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14 In order to demonstrate the beneficial effects on MD symptoms, in some cases it might  
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16 be useful to define and to induce immune tolerance by SIT and avoiding the contact of all  
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18 identified antigens at the same time, instead of singularly.  
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21 In conclusion, we believe that the proper assessment of an allergic condition should be  
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23 included in the diagnostic workup of MD patients, at least in selected cases based on clinical  
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25 history, especially those with bilateral ear disease. This would avoid generic deprivation diets  
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27 [23] and could single out those who might benefit from a tailored immune treatment, in  
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29 association or not with the traditional pharmacological therapies.  
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**Table 1.** Standard data table of AAOHNS-CHE raw data

	Stage	FV	HT	WRS	FL
Baseline	3	4	67.5	100	5
2 years- follow-up	2	0	30.0	100	1

FV: Frequency of Vertigo, definitive episodes per month for the previous 6 months;

HT: Hearing Thresholds, pure-tone average in decibels;

WRS: Word Recognition Score (speech discrimination) in percent;

FL: Functional Level (1-6).

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**Figure 1.** Pure tone threshold and speech audiometry before (a) and after treatment at 2 years and a half of follow-up (b)

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**Figure 2.** TEOAE evaluation before (a) and after treatment (b)

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