Commentary

Therapeutic illusion: another frontier in Ménière's disease

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Idiopathic endolymphatic hydrops, often referred as Ménière's disease (MD) is characterized by episodes of vertigo, hearing loss, tinnitus, and aural fullness (1,2). It is often a challenge in diagnosis and description, mostly because of its variability, which can make it difficult to recognize, thus possibly delaying treatment (3). Hearing loss has been widely studied, a fact that inclusively supports its staging according to the different guidelines proposed (4). Vertigo attacks appear to be the factor that affects more the health related quality of life of these patients as such, the primary goal of treatment is to reduce the frequency, intensity and duration of these episodes (1,5).

There are several difficulties, any author must stand, when analyzing results obtained with any MD treatment proposed. Fluctuation nature of the disease, the high and unexpected spontaneous remission rate, the difficulty of including a control group of patients without any intervention and the lack of validated instruments related to vertigo outcomes (other than disability and quality of life measurements) are clear examples of such problems. Here lies the importance of an appropriate clinical trial design, in order to prevent those possible methodological errors.

The study here reviewed (6) comprise a multicentre, double blind, placebo controlled, three arm trial in 14 tertiary referral centers to analyze the efficacy of betahistine (BH) treatment in MD patients. So far, there are very few evidence-based studies available in the medical literature, and these kind of high quality trials are essential. For instance, in 2000, the Cochrane Ear, Nose and Throat Disorders group evaluated the efficacy of BH on MD patients: only six clinical trials met the criteria to be included in the meta-analysis not being possible to reach any objective result, due to the extreme heterogeneous methodology between the different included studies. Similar problems were encountered when the Cochrane Ear, Nose and Throat Disorders group evaluated the effect of diuretics in 2006 (with a later revision in 2010): at that point they were not able to include any single trial to the systematic revision. Furthermore, in 2011, the Cochrane Ear, Nose and Throat Disorders group was able to provide recommendations on the use of intra-tympanic steroids or gentamicin, based on just one single trial in the former and on two studies in the later.

Thus, the limitations of the evidence base for preventive strategies of vertigo spells in MD, were a major concern of the current study's authors, and taken into account when designing the methodology.

In the study here presented the participants received placebo, low dose BH (2×24 mg daily) or high dose BH (3×48 mg daily) over nine months. Number of attacks per month, duration and severity of vertigo spells, change in quality of life scores and different audio-vestibular function parameters were the outcome of the study.

Interestingly the incidence of the vertigo spells, after treatment, did not differ between the three groups. The other results were consistent for all secondary outcomes with no significant differences between the placebo, low and high dose BH groups.

The study provides a proof to the different types of vertigo that patients with MD suffer. We are especially interested and concerned in those that occur spontaneously without any prior provocative event in particular, positioning. As has been previously shown in patients with MD, vertigo attacks provoked by a positional change can occur and they have a straightforward, non-medical but repositioning maneuver, treatment that has shown to be

extremely effective (7). In regards to vertigo spells, the participants in the study are interestingly homogenous for the three arms in terms of activity of the disease as the authors required at least the patient to suffer two episodes of vertigo per month (spontaneously appearing, not positionally provoked) before being included in the study. Taking that into account the mean number of dizzy spells per month was 5.1 (high dose), 5.8 (low-dose) and 6.2 (placebo). This number raises some concern on the type of attacks for three reasons. First, because they were taken from a one month follow-up in treatment, not retrospectively. Second, because of the high numbers which indicate that it was a very disabled population. In regards to the first question data is used usually prospectively during the follow-up of patients however, final adherence to established guidelines for the follow-up is usually incorrect in up to 50% of published papers (8); as such the evaluation with a diary is a probably more robust method not easily used (in the timing used by the authors) in other methods of treatment (intra-tympanic gentamycin, surgery). Regarding the second concern the authors have segregated the number of dizzy spells which could be defined as "true MD dizzy spell"; and the number is of sufficient nature as to consider the patients in a moderate to high severity and results significant and to be taken into account.

That defines the fact that patients had to be in an active phase of the disease to be included in the study, with at least two or more definitive spontaneous episodes of vertigo of at least 20 minutes duration. However these inclusion criteria could became the underlying cause of a selection bias and third concern. The fluctuating nature of the disease together with the spontaneous remission rate, could somehow explain why all three groups had a similar decrease of the vertigo spells rate. The clinical course of the disease is cyclical and unpredictable. Actually, there are reports which provide data that even without therapeutic intervention, the vertigo spells decline along the time as vestibular function decreases.

Because the natural history of MD is one of remission and recurrence, selecting those patients with an active phase of the disease will invariably cause a significant decline of the vertigo episodes after the period of the inclusion, creating the illusion of a therapeutic efficacy.

The importance of including a placebo controlled group is crucial and one of the great pieces of the research, but may be insufficient to differentiate the effect of the treatment from the cyclical natural history of the disorder. Therefore, assessment of the efficacy of treatments for MD needs randomized approach, including a control (free of treatment) group. Without the former, the placebo effect could not be accurately assessed and differentiated from spontaneous remission and/or fluctuation of symptoms.

Since there are many observational studies that support a beneficial effect of BH on MD, we should raise the question whether bias alone can explain the large effects differences between observational and experimental studies. Further long term randomized, placebo controlled trials should be considered to confirm the authors' findings, and focus more specifically on identifying possible predictors for BH treatment.

After this paper many questions have been opened regarding the evaluation of different modalities of treatment for patients with MD. However we have to keep in mind that this was not an unexpected result for the doctors in charge of these patients. The severity of clinical manifestations as measured in the patients included in the study (number of dizzy spells and quality of life and disability measures) is again a very important point; many would consider as an alternative (or even first line) treatment the use of intraympanic steroids (9) or gentamicin (10) for them in order to provide a transitory or more prolonged period of time free of vertigo spells (11).

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Footnote

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