

## Clinical Study

# Migraine-Related Vertigo: Eight Years of Experience with Pharmacologic Prophylaxis

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In 2001, our dizziness unit elaborated a diagnostic-therapeutic protocol for patients affected by migraine-related vertigo (MRV). This protocol contemplated the selection from March 2001 to December 2009 of 98 patients affected by MRV out of 1357 consecutive patients who came to our dizziness unit and the administration of pharmacologic prophylaxis. The results obtained constitute the object of this prospective, observational study. The efficacy of a 6-month treatment was registered by the patients by means of a self-assessment questionnaire where the results were divided into 5 categories, and, in case of patients with recurrent vertiginous attack, we recorded the percentage of the reduction in the frequency of the attacks. Of the sixty-four patients who completed the treatment, 43 (67.2%) reported complete resolution or substantial control, and, of the 57 patients suffering from recurrent vertigo attacks, 44 (77.2%) reported a reduction in the frequency of the attacks of at least 50%.

## 1. Introduction

The relationship between migraine and vertigo has recently aroused the interest of many neurotologists and practitioners who manage patients suffering from dizziness. There are different epidemiologic studies which confirmed this relationship [1–7], and in the last few years, many authors have published studies which throw fresh light on a new concept of migraine as a cause of various forms of vestibular dysfunctions.

This new entity has been given different denominations as, for example, “migraine-associated dizziness” [8], “vestibular migraine” [9], “migraine-related vestibulopathy” [10], “migrainous vertigo” [5], “migraine-associated vertigo” [11], and “migraine-related vertigo (MRV)” [12].

The vestibular symptomatology is varied and not specific, including recurrent vertigo attacks, chronic dizziness, and positional vertigo.

Like all forms of migraine, this is a typically female pathology. Often there is no concomitance between episodes of headache and symptoms of dizziness [7, 11]. Some patients have been free from headache for years before developing

vertigo, and headaches are often replaced with vertigo around menopause [13]. Sometimes vertigo is the only migrainous symptom (“migraine equivalent”), and other symptoms are the only true migraine markers, such as family history of migraine, motion sickness, and aura phenomenon.

The neurotologic examination is unremarkable, and totally negative reports have been described during symptom-free periods [8] as well as peripheral and central vestibular abnormalities with no specificity [8–10, 14, 15].

Neurotologic abnormalities have been observed in migrainous, nondizziness patients and in dizziness migrainous patients with superimposable percentages [16]. This may suggest that migraine itself could affect the vestibular system with or without vestibular symptoms, and that the vestibular examination does not provide sufficient information to diagnose MRV.

The treatment includes lifestyle changes (dietary habits, avoiding stress, nicotine, irregular sleep patterns) and, if this is not enough, pharmacological therapy.

The efficacy of triptans in acute attacks of dizziness is not supported by final data [17].

TABLE 1: Evaluation questionnaire for prophylactic management.

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(1) Resolution (complete disappearance of symptoms)
(2) Substantial control (occasional mild symptoms, representing no longer a bother)
(3) Moderate control (symptoms still occurring as an annoyance, although no longer preventing the patient from going about normal work or social activities)
(4) Minimal control (some improvements of symptoms, still interfering with the patient's work or social activities)
(5) No improvement

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Several studies, which are often retrospective or not based on precise criteria, have reported good results with drugs commonly used for the prophylaxis of migrainous headache [18–24].

In 2006, we [25] published an observational prospective study where all patients considered as affected by MRV according to precise inclusion criteria underwent pharmacological prophylaxis followed by data evaluation.

The continuation of this study, with the addition of the data collected in the 4-5 following years, is the topic of this article.

## 2. Materials and Methods

At the Dizziness Unit, Department of Otorhinolaryngology, Azienda Ospedaliera “S. Maria degli Angeli”, Pordenone Italy, from March 2001 to December 2009, we selected 98 out of 1357 consecutive patients (7.22%) using the following criteria.

- (i) At least five vertigo attacks occurring in any period of time, or dizziness and/or positional vertigo appeared at least 6 months before entering the study.
- (ii) Past or present migraine according to the diagnostic criteria elaborated by Headache international Society [26], and/or evident family history of migraine and/or strong motion intolerance (current or in childhood).
- (iii) Other vestibular disorder accurately ruled out by clinical examination or, if requested, by appropriate imaging studies (computed tomography, magnetic resonance). A history of benign paroxysmal positional vertigo was not considered an exclusion criterion, provided that its resolution before 6 months preceding the enrolment was documented.

They underwent complete neurotologic examination with ocular movement records through infrared videoculoscopia, pure tone audiometry, and bithermal caloric tests with electronystagmography recording according to Hallpike-Fitzgerald criteria (44° warm and 30° cold, 250 mL water in 40 seconds). The patients underwent pharmacological prophylaxis using drugs commonly administered for migraine prophylaxis: beta blockers (propranolol, metoprolol), flunarizine, clonazepam, amitriptyline, and pizotifen. In each

TABLE 2: Assessment of frequency reduction of vertigo attacks.

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(1) Complete resolution
(2) >50% reduction of attacks
(3) <50% reduction of attacks
(4) Frequency unchanged

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case, the therapy was selected on the basis of the patient's characteristics and the drug properties. The treatment was prolonged for 6 months and was then gradually withdrawn. We started with a low dose of the drug and increased it stepwise till the therapeutic effect (optimal control of the symptoms) was achieved. If no response was obtained with the maximum dose or important side effects occurred with one of the drugs, we went on to replace the drug.

In case of women undergoing a therapy with estrogens, it was recommended to suspend or reduce the dose of the drug and, if good results were achieved within two months, it was continued for 6 months, and the degree of efficacy was assessed as for any other pharmacological treatment.

The therapy was regarded as unsuccessful only after one month had elapsed.

After a therapy of 6 months, the patients evaluated the results, either directly or through phone interviews, through a questionnaire (Table 1) given within 3 months after the termination of the therapeutic trial. For those pts with recurrent attacks of vertigo another questionnaire was given in order to evaluate any changes in the frequency of the attacks (Table 2).

## 3. Results

The patients' age ranged from 15 to 87 years (median age 50 yrs); 85 were women (86,7%) and 13 were men (13,3%).

Eighty-nine patients (90,8%) reported migraine (at present or in the past) according to the diagnostic criteria of the International Headache Society (25), sixty-eight patients (69,3%) reported family history of migraine, and fifty-four (55,1%) reported motion sickness.

The onset of the dizziness symptoms ranked from 6 months to 30 years (6 years on average).

43 patients (43,8%) reported chronic dizziness and/or positional vertigo; 86 patients (87,8%) reported recurrent vertigo attacks, 31 of them (35,3%) also experienced chronic dizziness or positional vertigo during the interictal period; 12 patients (12,2%) had only dizziness/positional vertigo.

The length of the vertigo episodes was less than 5 minutes in 26 patients (29,5%), 5–60 minutes in 11 patients (12,5%), 1–24 hours in 24 patients (27,3%), and more than 24 hours in 27 patients (30,7%).

Two patients reported two periods of different duration.

As to the frequency of vertigo episodes, 15 patients (17,1%) reported one or more attacks per day, 16 patients (18,2%) one or more attacks per week, 30 patients (34%) one or more attacks per month, and 27 patients (30,7%) one or more attacks per year. Two patients reported two different frequency patterns.

Twenty-three patients (23.5%) experienced great discomfort during head shaking test (HST) or positional tests, even though their neurotologic examinations were normal.

In one patient, the caloric test caused an attack of migrainous headache.

Of the 86 patients with acute recurrent dizziness, only 9 (10.4%) reported headache associated with the attack of dizziness and 6 (7%) reported aura prior to the attack.

The clinic neurotologic examination revealed spontaneous nystagmus in one patient (1.1%), 18 patients (18.4%) had positional nystagmus, vertical in two cases; HST showed nystagmus in 24 patients (24.5%), vertical in two cases; 66 patients (67.3%) had a normal neurotologic examination.

Bithermal caloric test was performed in 78 patients: in 8 patients (10.2%) the test showed only canal paresis (CP), in 9 patients (11.5%) only directional preponderance (DP), in 8 patients (10.2%) PC and PD combined, in 8 (10.2%) bilateral hyporesponsiveness, in 1 (1.3%) monolateral hyperresponsiveness, and in 46 patients (59%) the test showed no pathologies.

*Followup.* 34 patients (34.7%) did not complete the treatment. 10 were lost during the follow-up; 6 patients chose not to undergo the therapy because they did not trust the diagnosis or the need for therapy; 7 patients were not recommended by general practitioners or neurologists; two patients did not take the drug correctly; two patients stopped the treatment because of another pathology occurred; 3 patients stopped the treatment due to side effects caused by the drug, and they refused to replace it with another one contemplated in the protocol; in 4 cases, after an ineffective treatment with one drug, the patients did not want to continue with another drug contemplated in the protocol.

Sixty-four patients (65.3%) completed the trial successfully.

The first choice for the therapy was: Propanolol in 20 patients, Metoprolol in 2 patients, Clonazepam in 19 patients, Flunarizine in 18 patients, Pizotifen in 3 patients, and suspension of estrogenic hormones in 2 patients.

For 11 patients, we had to change the therapy (in 4 cases because of inefficacy and in 7 cases because of side effects). Propanolol was abandoned in 7 patients: in 2 due to inefficacy, and in 5 because of side effects (3 patients with symptomatic hypotension-bradycardia, 1 patient with impotency, 1 patient with antiprolactin effect).

Flunarizine was abandoned in 2 patients, both suffering from side effects (1 patient had hypotension, 1 showed an increase in appetite and body weight). Clonazepam and Pizotifen were abandoned due to inefficacy.

We must also consider the 7 patients out of follow-up who abandoned the treatment (on account of inefficacy or side effects) and refused to continue the therapy with another drug.

The drugs used were: Flunarizine in 3 patients, in 2 of them it was abandoned because of inefficacy, in 1 patient because of side effects (sleepiness); Clonazepam in 3 patients, in 1 of which it was abandoned due to inefficacy, in 2 patients because of side effects (1 patient sleepiness, 1 patient urticaria); Propanolol in 1 patient (inefficacy).

TABLE 3: Final therapy in 64 patients.

Propranolol	13 Pts	(dose range 40–160 mg)
Metoprolol	2 Pts	(dose range 100–200 mg)
Flunarizine	21 Pts	(dose range 5–10 mg)
Clonazepam	19 Pts	(dose range 0,25–1 mg)
Pizotifen	5 Pts	(dose range 0,50–0,75 mg)
Amitriptyline	2 Pts	(dose 10 mg)
Estrogenic hormones suspension	2 Pts	

On the whole, Propanolol was abandoned in 8 of 21 patients (38.1%); in 5 patients (23.8%) because of side effects and in 3 patients (14.3%) due to inefficacy.

Clonazepam was abandoned in 4 of 22 patients (18.2%); in 2 patients (9.1%) due to inefficacy and in the other two due to side effects. Pizotifen was abandoned in 1 case out of three.

The final therapy and the doses used in 64 patients are listed in Table 3.

After 6 months of therapy, the results were complete resolution of symptoms in 18 patients (28.1%), substantial control in 25 patients (39.1%), moderate control in 13 patients (20.3%), minimal control in 2 patients (3.1%), and no improvement in 6 patients (9.4%).

57 (89%) of the 64 patients who completed the therapy had recurrent attacks of vertigo. Of these 57 patients, 30 (52.6%) reported complete resolution of the attacks, in 14 patients the frequency of the attacks reduced of over 50%, in 7 patients (12.3%) the reduction was less than 50% and 6 patients (10.5%) showed no change in the frequency of the attacks.

#### 4. Discussion

When can a dizziness syndrome be actually defined as “migrainous”? This is the first issue we faced in 2001 when elaborating on our study protocol.

In the same year, Neuhauser et al. [5] suggested diagnostic criteria for “defined” migrainous vertigo (i.e., migraine according to the IHS criteria, migrainous symptoms during at least two dizziness attacks) and “probable” migrainous vertigo (i.e., migraine according to the IHS criteria, migraine symptoms during vertigo, migraine-specific triggering factors of vertigo, or response to antimigraine drugs).

The idea that the temporal relationship between headache and vertigo in the diagnosis of MRV is fundamental is not shared by many authors. Brantberg et al. [11] found that only half the MRV patients have never had a headache simultaneously with their vertigo attacks. Vuković et al. [7] reported that in one group of migraine patients who experienced vertigo in their lifetime, vertigo symptoms coincided with the migraine attack in only 23.2% of patients.

In our series, the temporal relationship between migraine symptoms and vertigo is somehow weaker, only 9 patients reported concomitant headache (10.4%) and 6 patients reported aura before vertigo (7%).

At present, unanimously accepted diagnostic criteria for MRV do not exist; MRV should be regarded as the diagnosis of exclusion.

When there is no evidence of any cause to explain vertigo symptoms in a migrainous patient, the MRV diagnosis could be at least regarded as probable, and, if necessary, one trial of antimigraine therapy is recommended. This is basically the criterion used in our work since 2001, with no changes.

The results reported in our previous article have been substantially confirmed by the data collected in a larger series of patients.

As regards the epidemiologic data, the percentage of patients affected by MRV one 7.22% of all vertiginous patients (previously 8.13%), and the percentage of female gender is 86.7% (previously 84.9%).

In patients with recurrent attacks of vertigo, the type of attacks was classified according to frequency, and length has no predominant temporal pattern.

About two thirds of the patients have a normal neurotologic examination and caloric test.

Twenty three of 66 patients whose neurotologic examinations were normal (i.e., more than one third) reported strong malaise while they underwent tests requiring the performance of quick and repeated movements of the head, as HST and/or positional tests.

These results, which in our experience are not common in other patients with normal neurotologic examinations, might indicate a condition of “hypersensitivity” of the vestibular apparatus in migraine patients.

Once more, we have found scarce compliance with the prophylactic treatment; 34.7% of the patients did not complete the treatment. Undoubtedly this evidence can be attributed to the type of treatment (long duration, possible side effects, sometimes long latency of the effect of the drug). Anyway, we must also take into special consideration that four years after our previous work, scepticism in accepting the MRV as a clinical entity is still spread among patients and doctors, at least in the Italian context of medical practice.

Some of the patients who did not complete the treatment may have been induced to suspend the therapy because there was no initial response to the treatment. These data, even without considering part of the negative results, might represent a bias when analysing the results.

The drugs chosen are the ones for which literature has been providing evidence of use in the prophylaxis of migrainous vertigo for many years.

Among the three most frequently used drugs (i.e., Propanolol, Flunarizine, Clonazepam), Propanolol seemed to produce side effects more frequently: in 5 cases out of 21, it was abandoned because of side effects (23.8%), as opposed to the 3 out of 21 cases using Flunarizine (14.3%), and 2 of 22 cases (9.1%) in which Clonazepam was used, although the limited nature of the series does not allow any statistically significant conclusion.

## 5. Conclusions

MRV as an entity is widely accepted by all neurotologists, anyway, it is hardly possible to give an exact definition.

The lack of diagnostic commonly accepted criteria and the heterogeneous clinical expressions made the results of many descriptive works and therapeutic trials rather aleatory.

Since 2001, we have selected out of all the patients admitted to our dizziness unit the ones affected by MRV according to the same inclusion criteria.

We registered clinical manifestations and neurotologic features, treated patients with pharmacologic prophylaxis, and analysed the results using a standardized method.

The data obtained from pharmacologic prophylaxis shows the efficacy of this procedure, 67.2% of the patients achieved satisfactory control of the symptoms (complete resolution plus substantial control), and 77.2% of the patients with recurrent attacks of dizziness had a reduction in the frequency of at least 50%.

While we await well-defined diagnostic and therapeutic protocols, our approach can offer an optimal compromise between diagnostic congruence and the need to provide a therapeutic alternative for these patients in which vertigo often falls under the broad category of “idiopathic” vertigo.

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