Management of vestibular migraine

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Abstract: Vestibular migraine is considered to be the second most common cause of vertigo and the most common cause of spontaneous episodic vertigo. The duration of attacks varies from seconds to days, usually lasting minutes to hours, and they mostly occur independently of headaches. Long-lasting individual attacks are treated with generic antivertiginous and antiemetic drugs. Specific antimigraine drugs are unlikely to be very effective for rescue. The mainstay of the management of vestibular migraine is prophylactic medication. To date, there are no controlled trials available; the body of knowledge builds on case series and retrospective or observational studies. Most drugs are also used for the prevention of migraine headaches. The choice of medication should be guided by its side effect profile and the comorbidities of patients. Betablockers such as propanolol or metoprolol are preferred in patients with hypertension but in the absence of asthma. Anticonvulsants include topiramate when patients are obese, valproic acid and lamotrigine. Lamotrigine is preferred if vertigo is more frequent than headaches. Calcium antagonists include verapamil and flunarizine. If patients have anxiety, tricyclic antidepressants such as amitryptiline or nortryptiline or SSRIs and benzodiazepines such as clonazepam are recommended. Acetazolamide is effective in rare genetic disorders related to migraine-like episodic ataxia; however, its place in vestibular migraine is still to be established. Nonpharmacological measures such as diet, sleep, hygiene and avoidance of triggers are recommended as they are for migraine. Vestibular rehabilitation might be useful when there are complications such as loss of confidence in balance or visual dependence.

Keywords: migraine, vestibular, prophylaxis, beta-blockers, anti-convulsants

Introduction

The association of migraine and vertigo has been recognized for a long time but the nature of this relationship is uncertain in the absence of reliable biomarkers.

Without exception, case–control studies have found an association between migraine, vertigo and dizziness beyond chance. Significantly more patients with migraine have vertigo compared with patients with tension-type headache [Kayan and Hood, 1984] and headache-free controls [Vukovic *et al.* 2007]. In a German study the lifetime prevalence of migraine in the general population was found to be about 14% and the lifetime prevalence of vertigo 7% [Neuhauser *et al.* 2005], resulting in a chance coincidence of 1%. The co-occurrence of vertigo and migraine, however, was found to be 3.2%.

The association between migraine and vertigo corresponds to the generally recognized condition basilar-type migraine only in a minority of cases. Various terms have been used to describe recurring vestibular symptoms in migraine when an alternative diagnosis has been ruled out, such as migraine-associated dizziness, migraine-related vestibulopathy, migrainous vertigo and vestibular migraine. The latter terms imply a causal link between migraine and the vestibular symptoms, which is an assumption based on epidemiology [Lempert and Neuhauser, 2009; Neuhauser *et al.* 2006] and on abnormalities in vestibular tests during and between vertigo episodes [von Brevern *et al.* 2005; Furman *et al.* 2003]. In this article the terms migrainous vertigo and vestibular migraine will be used interchangeably.

The development of operational diagnostic criteria for migrainous vertigo [Furman *et al.* 2003; Neuhauser *et al.* 2001] was an important step in bringing together diagnostic standards for a condition lacking biomarkers. The presentation

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of vestibular migraine varies. Symptoms include spontaneous and positional vertigo, head motion vertigo/dizziness and ataxia of variable duration, ranging from seconds to days. Most episodes have no temporal relationship with the headaches.

The pathophysiology of vestibular migraine has not been established. Observations carried out during episodes and interictal eye movement abnormalities suggest that it is a central vestibular disorder, but peripheral vestibular causes have also been discussed [von Brevern *et al.* 2005; Dieterich and Brandt, 1999; Baloh, 1997]. Except for basilar-type migraine an 'aura-type' mechanism is hypothetical. Cortical spreading depression is assumed to be the mechanism for migraine aura and in theory this mechanism is also possible in the cerebellum [Vincent and Hadjikhani, 2007]. The vascular theory of migraine is no longer considered valid; instead migraine is considered to be a brain disorder [Goadsby, 2009; Goadsby *et al.* 2009]. For vestibular migraine the concept of an ion-channel disorder is particularly interesting because different mutations of the *CACNA1A* gene coding for a transmembrane component of a neuronal calcium channel can provoke familial hemiplegic migraine or episodic ataxia type 2 [Jen *et al.* 2004]. However, several candidate genes coding for ion-channel proteins have not been found in a population with vestibular migraine [von Brevern *et al.* 2006].

Successful treatment depends on adherence to recommendations. A first obstacle may be patients accepting their diagnosis. This is difficult when diagnosis is based on symptoms and without an independent diagnostic standard. This problem applies to migraine in general, although the condition is well known [Evans and Evans, 2009], and even more so to vestibular migraine. As most vestibular episodes are temporarily independent of headache it often seems illogical for patients to link them with migraine. In addition, patients might have heard contradictory interpretations of vestibular symptoms because it is still a controversial subject in the medical community [Philips *et al.* 2010]. Recent reviews on the treatment of vestibular migraine are available [Cha, 2010; Fotuhi *et al.* 2009; Marcus *et al.* 2003].

Treatment of the individual attack

The duration of individual attacks of vestibular migraine varies widely from seconds to weeks, but mostly they last from minutes to hours [Eggers, 2007]. In the case of prolonged attacks, a symptomatic rescue treatment could be considered.

To treat an attack of migrainous vertigo the general principles of treatment of acute vertigo also apply. Acute antivertiginous and antiemetic drugs are considered useful for suppressing vestibular symptoms [Baloh, 1997], such as promethazine 25 or 50 mg which combines antivertiginous, antiemetic and sedating properties, and metoclopramide which helps to control the nausea and vomiting associated with both headache and vertigo, promotes normal gastric motility and may improve absorption of oral drugs. Antihistaminic drugs such as dimenhydrinate and meclizine are useful for treating milder episodes of vertigo and for controlling motion sickness.

But are there any specific treatments for vertigo attacks of migrainous origin?

Some trials have been done with triptans. In a retrospective study based on patient records, sumatriptan was found to be efficient when the vestibular symptoms were linked or not linked to the headache [Bikhazi *et al.* 1997].

A placebo-controlled study with zolmitriptan included 10 patients who had a total of 17 attacks. This study however was inconclusive because of limited power and the response rate for the primary outcome of clear relief of symptoms after 2 h was relatively low: 38% for zolmitriptan *versus* 22% for placebo [Neuhauser *et al.* 2003].

Although it has not been established whether the migraine aura mechanisms also apply to the vestibular symptoms of migraine, it is interesting to look at studies specifically targeting the treatment of migraine auras. Sumatriptan 6 mg administered subcutaneously was found to be ineffective in shortening visual auras and was ineffective in preventing headache if taken during the aura [Bates *et al.* 1994]. A pilot study suggests that rizatriptan does not consistently reduce visually induced motion sickness in people with migraine but may diminish motion sickness potentiation by cranial pain [Furman and Marcus, 2009].

Ergots are not recommended for the treatment of migraine preceded by major aura because of

potential vasoconstriction [D'Andrea et al. 2003]. They are also contraindicated in people with hemiplegic and basilar-type migraine [Silberstein and McCrory, 2003]. Probably for these reasons, ergots have not been used to treat episodes of vestibular migraine.

The calcium antagonists nimodipine [Jensen et al. 1985] and nifedipine [Hoffert et al. 1992] have been shown to be ineffective in shortening the aura or preventing headaches and have not been used to treat migrainous vertigo attacks.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have so far only been reported in one study [Bikhazi et al. 1997] to be useful in treating individual vertigo attacks but not for migraine aura [D'Andrea et al. 2003].

Other drugs used to successfully treat migraine aura but that so far have not been reported for attacks of vestibular migraine are furosemide [Rozen, 2000] and acetazolamide [Haan et al. 2000] for visual aura status. None of the seven patients had responded to valproate or propranolol.

It seems that drugs effective in treating migraine headache (triptans, NSAIDs) do not work as well for vertigo, or might even be hazardous according to the warnings for aura treatments (ergots). Therefore if individual attacks need to be treated it would be safer to use a generic strategy with symptomatic drugs to relieve vertigo and nausea, as in other causes of acute vertigo. Potentially interesting drugs for acute attacks of vestibular migraine that so far have not been reported are furosemide and acetazolamide.

Prophylactic treatment

Episodes of vertigo are often relatively short and/ or frequent [Dieterich and Brandt, 1999]. Therefore treating individual episodes is not a viable option and prophylactic strategies should be considered. Before discussing such strategies with patients it is important they accept the diagnosis of vestibular migraine for good adherence to treatment.

Nonpharmacological measures

General recommendations for migraine headache prophylaxis, such as diet, sleep hygiene, avoidance of trigger factors, are probably also beneficial for migrainous vertigo [Reploeg and Goebel, 2002]. Biofeedback methods have been reported for other kinds of equilibrium problems or vertigo [Shutty et al. 1991] but to date such studies have not been reported for vestibular migraine.

Vestibular rehabilitation

Physiotherapy plays an important role in the management of vestibular conditions. This is mainly targeted at the compensation of unilateral vestibular deficits, strategies to cope with bilateral deficits, repositioning manoeuvres for benign positional vertigo, and rehabilitation of complications such as visual dependence. In fluctuating disorders such as Menière's disease and vestibular migraine the value of vestibular rehabilitation is not so well established.

A retrospective chart review of 14 patients with migraine-related vertigo and migraine headache demonstrated improvement in physical performance measures and self-perceived abilities after vestibular physical therapy [Whitney et al. 2000]. Patients with vestibular disorders with or without a history of migraine (30 in each group) demonstrated improvements in both subjective and objective measures of balance after physical therapy [Wrisley et al. 2002].

Physiotherapy seems to be particularly useful for complications of vestibular migraine such as anxiety, visual dependence or loss of confidence in the balance system [Furman et al. 2005]. However, studies have not investigated if this intervention can reduce the frequency or severity of vestibular episodes.

Pharmacological prophylaxis

Prophylactic medication in migraine has an important role if attacks are frequent or insufficiently controlled by rescue medication, and seem to converge on two targets: inhibition of cortical excitation and restoring nociceptive dysmodulation [Ramadan, 2007]. In vestibular migraine prophylactic drug treatment is considered the mainstay of medical management, although controlled studies are largely lacking. The drugs used are often those also used for the prevention of migraine headaches, such as betablockers, calcium antagonists, anticonvulsants and antidepressants.

Two studies have reported data on a stepwise approach to treatment with various drugs, moving on to the next step if a drug is not tolerated or inefficient. In one study [Maione, 2006] the sequence of drugs was a betablocker (propanolol or metroprolol) followed by flunarizine, clonazepam and finally amitryptiline, eventually finding substantial relief for vestibular symptoms and headaches. In another study [Reploeg and Goebel, 2002] the steps were dietary intervention followed by nortryptiline followed by atenolol. Diet alone helped 13 of 81 of patients, diet plus an antidepressant helped 24 of 31 and diet, antidepressant and a betablocker (atenolol) helped 21 of 37. Parallel responses to headache and vertigo were observed in 95% of patients.

Three studies reported observations when several drugs were used, either as monotherapy or in combination. In a retrospective review of 89 patients diagnosed with migraine-related dizziness or vertigo, 79 were treated pharmacologically [Johnson, 1998]. Drugs used included benzodiazepines in 90% (mostly clonazepam), tricyclic antidepressants in 42% (amitryptiline or nortryptiline), betablockers in 35% (propanolol), selective serotonin reuptake inhibitors in 7.6% of patients (fluoxetine, sertraline or paroxetine) and calcium-channel blockers (verapamil or diltiazem) in 7% of patients. With this approach, a substantial response (defined as improvement of symptoms such that they would no longer interfere with daily activities) was seen in 92% of patients with episodic vertigo, 89% of patients with positional vertigo, and 86% of patients with nonvertiginous dizziness. None of the patients responded to the calcium antagonists used. At the moment of improvement, 44% of patients were receiving one drug, 33% were receiving two drugs and the remainder were receiving between three and six drugs.

A survey of 58 patients in a headache clinic with a history of dizziness or vertigo [Bikhazi *et al.* 1997] found that prophylactic medications targeting the treatment of headache (beta-blockers, calcium-channel blockers, tricyclic antidepressants — individual substances not specified — or methylsergide, valproic acid, cyproheptadine) were also effective in treating the vertigo and dizziness. Responses were graded from 1 to 4, with 4 being the most effective treatment, and were based on patients' recall of the effectiveness of the therapeutic intervention. A median efficacy score of 2 for treating migraine headaches was found and 1 for treatment of vertigo or dizziness. The temporal relationship between the dizziness and the migraine headache did not influence therapeutic efficacy.

In a retrospective study of 100 patients [Baier *et al.* 2009], 26 received nonpharmacological intervention and 74 received drugs, mainly betablockers (propanolol or metropolol), anticonvulsants (valproic acid, topiramate or lamotrigine), or butterbur root extract. The study reported a reduction of frequency, duration and severity of vestibular attacks as well as headaches. The effect was more marked for the pharmacological treatments.

In a randomized, double-blind, placebo-controlled, crossover design study [Gordon *et al.* 1993], sodium valproate did not affect vestibulo-ocular responses in a rotatory chair test or vestibular complaints, but was effective in reducing migraine attacks in 8 of 12 patients.

Celiker and colleagues treated 37 patients with migraine (13 with vertigo, 13 with dizziness, and 11 without vestibular symptoms) with valproic acid (500 mg/day) for 3 months. Improvements were found in migraine and vertigo/dizziness frequency but not electronystagmographic findings [Celiker *et al.* 2007].

A study of topiramate 100 mg in 10 patients observed a remission over an average follow-up period of 9 months [Carmona and Settecase, 2005]. A retrospective study of 19 patients treated with lamotrigine 25 mg every morning for 2 weeks, then 50 mg for 2 weeks, to reach a target dose of 100 mg after weeks showed a significant reduction in the vertigo but not in headache frequency [Bisdorff, 2004].

In a case report study of 16 patients with the controversial condition chronic migrainous vertigo [Waterston, 2004], patients were treated with pizotifen, propanolol, verapamil or dothiepin. The study reported either complete resolution or marked improvement in both headache severity and vertigo.

Five patients with a familial syndrome of migraine, vertigo and tremor showed a marked decrease in the frequency of headaches, vertigo spells, and the severity of tremor when treated with acetazolamide [Baloh *et al.* 1996].

Studies on the prophylaxis of migraine aura, migraine with aura or basilar-type migraine

Although the mechanism behind the vestibular symptoms of migraine has not been established, it is reasonable to hypothesize a similarity to other neurological (nonpain) symptoms in migraine. Most studies of migraine focus on the headache as the main outcome or do not distinguish between migraine with and without aura [American Academy of Neurology, 2000; Mulleners and Chronicle, 2008], but some studies report more specifically on aura.

Several studies have shown the efficacy of lamotrigine on migraine with aura [D'Andrea *et al.* 1999] with an effect not only on visual aura but also on sensory, motor, phasic [Lampl *et al.* 1999] visual, basilar and hemiplegic [Pascual *et al.* 2004], and basilar-type migraine [d'Onofrio *et al.* 2007]. In a controlled 3-year prospective open study of 59 patients, lamotrigine was highly efficient in treating all types of aura (vertigo not specified) and headaches [Lampl *et al.* 2005]. In a report of two cases of persistent visual aura, lamotrigine was reported to be effective [Chen *et al.* 2001].

In a small study of 12 patients with migraine with aura, topiramate was not effective for treating aura but was for headaches [Lampl *et al.* 2004]. In a double-blind study of children with basilar-type migraine, topiramate was effective. No separate reporting on the aura symptoms was carried out [Lewis and Paradiso, 2007]. An observational study over 6 months in 16 patients with migraine with aura found levitiracetam had a positive effect on aura and headaches [Brighina *et al.* 2006].

A recent Cochrane review on anticonvulsants in migraine prophylaxis [Mulleners and Chronicle, 2008] found valproate and topiramate to be superior to placebo, acetazolamide, clonazepam, lamotrigine and vigabatrin were not better than placebo, and reported inconclusive results for gabapentine. In this review no distinction was made between migraine with and without aura.

The studies reported above seem to suggest a differential effect for some drugs on headaches *versus* aura symptoms. There also seems to be a tendency for anticonvulsants who are effective in treating aura to have more potential for treating vestibular migraine. This suggestion is also supported in an experimental study in which lamotrigine was superior to valproate and riboflavin in suppressing cortical spreading depression in the rat [Bogdanov *et al.* 2010].

In a controlled trial patients with migraine received acetazolamide and this drug was found to be ill tolerated and not effective [Vahedi *et al.* 2002]. However, in a pilot study [De Simone *et al.* 2005] efficacy of acetazolamide was more marked for migraine with aura rather than without aura. Therefore acetazolamide seems to have a differential effect on pain and aura. This drug might also have more potential for treating vestibular migraine than shown so far on a small scale, or for very specific indications such as episodic ataxia.

Studies with metoprolol specifically looking at the effect on visual aura have shown inconclusive effects [Hedman *et al.* 1988].

A new look at studies on benign recurrent vertigo

The term vestibular Menière was not included in the second revision of the American Academy of Otolaryngology Head and Neck Surgery Committee on Hearing and Equilibrium criteria for Menière's disease and the differential diagnosis of vestibular migraine was not discussed in their document [Monsell *et al.* 1995]. The terms vestibular Menière's, recurrent vestibular vertigo and benign recurrent vertigo are used interchangeably. Recent studies show that benign recurrent vertigo is very strongly associated with migraine and usually does not evolve to become Menière's disease [Cha *et al.* 2009; Baloh, 1997] and so many of these cases might now be considered to be vestibular migraine.

Controlled studies have extensively investigated betahistine, a histamine analogue, and flunarizine, a calcium antagonist, to treat recurrent vertigo and shown them to be efficient [Albera *et al.* 2003; Deering *et al.* 1996; Fraysse *et al.* 1991; Toddand Benfield, 1989; Elbaz, 1988; Olesen, 1988; Oosterveld, 1984, 1982]. The observations on flunarizine are consistent with those for vestibular migraine, whereas betahistine is still considered a classical drug for Menière's disease, but it might also relieve the vestibular symptoms of migraine.

Psychiatric comorbidity

The relationship between anxiety and vertigo is complex. On the one hand, anxiety can be a

primary cause of vertigo (a defining symptom in panic attacks) but on the other hand, anxiety is often a secondary complication of vertigo [Staab and Ruckenstein, 2003; Pollak *et al.* 2003]. An additional complication is the well recognized comorbidity of migraine with depression and anxiety [Torelli and D'Amico, 2004; Härter *et al.* 2003; Breslau *et al.* 1994].

Vestibular migraine and Menière's disease seem to be the vestibular disorders with the highest risk of secondary psychiatric complications, mainly anxiety [Eckhardt-Henn *et al.* 2008]. Along this line, the term 'MARD' (migraine–anxiety related dizziness) was proposed [Furman *et al.* 2005].

In patients with MARD in whom balance symptoms predominate, a combination of an antidepressant, such as imipramine, and a benzodiazepine, such as clonazepam, is recommended by the authors. For patients with MARD in whom anxiety symptoms predominate, a selective serotonin reuptake inhibitor, such as paroxetine or sertraline, is preferred. Vestibular rehabilitation might be beneficial, particularly in patients with additional space and motion discomfort.

Conclusions

Vestibular migraine is largely accepted in the vestibular community and probably represents the second most common cause of vertigo after benign positional vertigo [Lempert and Neuhauser, 2009; Neuhauser *et al.* 2006], by far exceeding Menière's disease. Only in 2003 the first operational definition of vestibular migraine was proposed [Furman *et al.* 2003], which was an important step for conducting comparable research on epidemiology, natural history, pathophysiology and treatment.

The quality of the data on vestibular migraine management is still relatively poor, despite its enormous importance in daily practice. Studies published before 2003 used variable definitions of vestibular migraine and only a few were controlled. Some studies report data on a pragmatic approach to treating vestibular migraine using multiple drugs; others have focused on using only one drug. At this stage it is not possible to quantify the effects of the treatments proposed but some recommendations can be made.

The first step should always be to give the patient a diagnosis and for the patient to accept this diagnosis. Although the condition can have a considerable psycho-social impact, it is medically benign and some patients are happy to receive an explanation for their symptoms and do not ask for treatment. However, treatment is often required and the choice of drugs is mainly guided by the frequency of the attacks and the side effect profile.

Rare and long vestibular spells would call for rescue medication only; frequent and/or short episodes would require a prophylactic approach.

It is important to consider comorbidities, such as arterial hypertension or hypotension, anxiety and depression, asthma and body weight, and to establish if vertigo and headaches are equally distressing or whether one is more pronounced than the other.

If quick relief is needed, a calcium antagonist (flunarizine or verapamil) is a good option, but be aware of sedation and weight gain. Also, in the case of prolonged treatment, watch out for extrapyramidal side effects and depression for flunarizine.

When there is coexisting hypertension, a beta-blocker should be considered if bronchospasm or bradycardia is not a problem. If headaches are prominent consider the anticonvulsant topiramate in obese patients and valproate in nonobese patients, or betablockers.

When there is coexisting sleep disturbance and anxiety consider amitryptiline or nortryptiline. If psychiatric symptoms are prominent, benzodiazepines, serotonin reuptake inhibitors and/or a referral to a psychiatrist or behavioural therapist should be considered. If headache is rare compared with vertigo and/or the vertigo is part of an aura, lamotrigine could be given as first choice.

Acetazolamide is a potentially interesting drug for vestibular migraine. So far this drug has mainly been observed to be highly effective for episodic ataxia and a familial syndrome of migraine, vertigo and tremor.

Referral to vestibular rehabilitation should be considered for all patients, particularly if secondary complications such as deconditioning, loss of confidence in balance or visual dependence have developed.

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