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從臨床流行病學與神經耳科學來探討與偏頭痛相關之眩暈及頭暈

Clinical Epidemiological and Neurotological Approaches to Migraine-related Vertigo and Dizziness

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Table of Contents

Figures

Tables

Abstract

Objective This study was designed to analyze the clinical manifestation of patients with migraine-related vertigo and dizziness, and explore the association between clinical characteristics and treatment effectiveness. The relationships between different diagnostic groups were investigated as well.

Method The source population was comprised of patients visiting a vertigo special clinic from July 2007 to January 2008. Subjects with other potential diagnoses were excluded. Inclusion criteria consisted of ≥ 5times of migrainous headache and ≥ 2 times of vertigo/dizziness episodes. One-hundred and ten subjects were enrolled and eligible for this study. All the patients received structured interview of clinical presentations, and the results of audiovestibular function tests were recorded. Further classification of study subjects were based on the diagnostic criteria of basilar type migraine (BtM), definite migrainous vertigo (dMV) and probable migrainous vertigo (pMV). Excluding 7 subjects lost from clinic, treatment effectiveness was evaluated in 103 subjects after a consecutive 3-month medication.

Result The demographic characteristics constitute a mean age of 40 years old, female predominance (85%), strong family preponderance (72%), plateau of onset of symptoms around 20-29 years old, and headache as the first presenting symptom in 61% of subjects. Migraine precipitants were identified in 106 subjects (96%).

Significant factors associated with poor response are: younger age at presentation (adjusted odds ratio (aOR) =2.38 for each 10-year decline, 95% confidence interval (CI): 1.39 ~ 4.07), frequent vestibular episodes (aOR=7.73, 95% CI: 2.05 ~ 19.1), and abnormal optokinetic nystagmus (OKN) tests (aOR=5.40, 95% CI: 1.60 ~ 18.2). Food precipitation showed borderline correlation with treatment response (aOR=0.31, 95% CI: 0.09 ~ 1.04). Furthermore, BtM and dMV group are similar in clinical presentation, e.g. migrainous symptoms, motion sickness and sequential relationship between migraine and vertigo, but differs in that BtM had more extensive neurological symptoms, more frequent vestibular symptoms, more central signs on electronystagmography tests, and also, the worst treatment effectiveness. In contrast, pMV group represents the least severe clinical manifestation.

Conclusion This study enrolled a representative sample of migraine-related vertigo and dizziness in Taiwan. The significant factors in relation to treatment effectiveness are identified, i.e. frequency of vestibular episodes, age at presentation, and OKN abnormalities. The relationship between these three diagnostic groups is most likely a distribution of severity across the disease spectrum, with BtM presenting the most extensive involvement of the brainstem and the worst treatment response.

Keywords: migraine, vertigo, dizziness, treatment, optokinetic nystagmus.

中文摘要

目的 本研究之主要目的爲分析與偏頭痛相關之眩暈及頭暈患者之臨床表現，並尋找與治療效果相關之因子。此外，一併探討不同診斷疾病群間之關係。

方法 病患來源爲自 2007 年 7 月至 2008 年 1 月於耳鼻喉科眩暈特別門診就診之病患，所有病患均接受一系列之檢查並排除其他可能之診斷。研究之收案條件爲 5 次以上之偏頭痛與 2 次以上之前庭症狀，計 110 名病患納入本研究。每位患者都接受制式化的當面訪談，並收集相關之臨床症狀與檢查結果，再依據基底型偏頭痛 (BtM)、確定偏頭痛型眩暈 (dMV)、與疑似偏頭痛型眩暈(pMV)之診斷基準進行分類比較。除了 7 名患者未完成治療與追蹤外，其他病人均接受藥物治療爲期三個月，結束後依病歷記載分析其治療結果。

結果 病患之平均年齡爲 40 歲，多數爲女性（85%）且有偏頭痛之家族史（72%），症狀發作之年齡大多介於 20 至 29 歲之間，且 61%之患者以頭痛爲初始表現。106 位（96%）患者均表示有一種以上之偏頭痛誘發因子。與治療結果相關之因子爲年齡 (年齡每小 10 歲之危險性爲 2.38 倍，95%信賴區間： 1.39 ~ 4.07)，前庭症狀之發作頻率 (危險性=7.73, 95%信賴區間：2.05 ~ 19.1)，以及異常的視運動眼振測驗 (危險性=5.40, 95%信賴區間： 1.60 ~ 18.2)。此外，BtM 與 dMV 兩組之臨床表現相似，包括偏頭痛之相關症狀、動暈症、以及頭痛與頭暈間之時序性，但 BtM 組有較多神經學症狀與較頻繁之發作頻率，且眼振電圖檢查出現較多中樞性徵象。反之，pMV 組則屬病症最輕微。

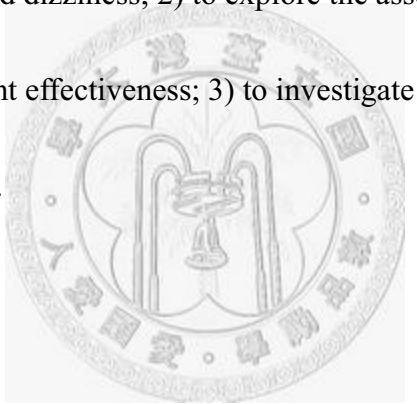
結論 本研究收集了與偏頭痛相關之眩暈及頭暈在台灣地區之代表性族群，且臨床表現與文獻之記載相符。與治療結果相關之重要因子包括年齡、前庭症狀之發作頻率與異常之視運動眼振測驗。三組不同診斷疾病群之間的關係可能意味此一症候群在臨床嚴重度的不同，其中基底型偏頭痛之症狀最爲嚴重且治療成果最不理想。

關鍵詞：偏頭痛、眩暈、頭暈、治療、視運動眼振

1. Introduction

The association between migraine and vertigo has been noted since the early days of clinical experiences. Bickerstaff (1961) coined the term “basilar artery migraine” to describe adolescent females with transient neurological deficits in posterior circulation followed by occipital headache, nausea and vomiting. Subsequently, several case series presented the clinical manifestations of migraine associated vestibulopathies using different terms, e.g. benign recurrent vertigo or migraine associated dizziness (Slater, 1979; Cutrer and Baloh 1992). In 1988, the International Headache Society (IHS) first published the diagnostic criteria for basilar artery migraine, which required migrainous headache coupled with two or more auras. An updated edition (IHS, 2nd edition, 2004) changed the term to “basilar type migraine” (BtM) due to the uncertain involvement of basilar artery territory. Conceptually, the IHS criteria for BtM regard vertigo as an “aura” of posterior circulation; hence, the clinical presentation of vertigo must meet the following criterion: 5-60 minutes of vertiginous episodes, followed by migrainous headache within 60 minutes. Since clinical presentations of vestibular symptoms are highly variable, many cases do not meet the IHS criteria. Alternatively, various diagnostic criteria such as migraine-related vestibulopathy, vestibular migraine and migrainous vertigo have been proposed (Cass, et al., 1997; Dieterich and Brandt, 1999;

Neuhauser, et al., 2001). Of these, the operative diagnostic guides for definite migrainous vertigo (dMV) and probable migrainous vertigo (pMV) are widely recognized. Population based survey in German (Neuhauser, et al., 2006) had revealed a 0.98% lifetime prevalence of definite migrainous vertigo. However, the relationship between these criteria remained unclear. Furthermore, the correlation between these complex clinical manifestations and therapeutic outcome was still unknown. Hence, this study was conducted 1) to describe the clinical manifestation of patients with migraine-related vertigo and dizziness; 2) to explore the association between clinical characteristics and treatment effectiveness; 3) to investigate the relationship between different diagnostic groups.



2. Literature review

2.1 Clinical presentation

Although the concept of migraine-related vertigo is growing widely accepted in recent days, the original study concerning this study was only several decades ago. In 1961, Bickerstaff reported his clinical experience of 34 patients, which demonstrated a female predominance, with all the subjects under age 35. He noted that subjects experienced transient neurologic symptoms, e.g. vertigo, ataxia, dysarthria, tinnitus and bilateral paresthesia, which lasted for 2-45 min and followed by occipital headache. The headache was usually throbbing in character with a close relationship with menstruation period. In the mean time, 28 out of 35 subjects had positive family history of headache. He attributed these clinical features to transient ischemia of posterior circulation and hence coined the term: “basilar artery migraine”. Later on, Basser (1964) reported 17 pediatric cases, who suffered from sudden vertigo attack without associating headache, and proposed the term: “benign paroxysmal vertigo of childhood (BPVC)”. Follow-up study by Watson and Steele (1974) revealed that more than half of these children had developed migrainous headache and therefore, the term “migraine equivalent” was introduced. Subsequent studies had focused on the relationship between migraine and vertigo, aside from pediatric and adolescent patients. Slater (1979) reported 7 adults, who suffered from

sudden onset of vertigo precipitated by common precipitants of migraine, i.e. alcohol intake, lack of sleep, and emotional stress. He proposed the term “benign recurrent vertigo” and it had been widely used in clinical settings thereafter.

Further, several case-control studies had demonstrated a specific correlation between vestibular symptom and migraine, compared to other types of headache. For example, Kuritzky et al. (1981) conducted a series of 104 headache patients and 54 controls with a focus on the presentation of headache-free phase. He noted that classical migraineurs suffered more vertigo (42%) and motion sickness (42%) than controls (10% and 17%, respectively). Classical migraine is an old- fashioned term which mainly corresponds to “migraine with aura” in modern classification criteria. Kayan and Hood (1984) conducted another case-control study including 200 patients with migraine and 116 patients with tension headache serving as controls. He reported a similar result that more vertigo (26%) and motion sickness (51%) were noted in migraineurs, compared with tension headache subjects ($p<0.001$). In addition, latest studies by Neuhauser et al. (2001) enrolled 200 patients from dizziness and migraine clinics, and demonstrated a higher prevalence rate of migraine among dizziness group (38%) compared with age- and sex-matched control group (24%). These findings had certainly ensured the reciprocal association between migraine and vestibular symptom.

Subsequently, the clinical spectrum of vestibular symptom in migraineurs, including the temporal relationship between vertigo/dizziness and migraine, had received great attention on academic researches. In 1992, Cutrer and Baloh conducted a retrospective review of 91 subjects with “migraine associated dizziness” out of approximately 5000 patients referred to UCLA neurotological clinic. The duration of dizziness episodes ranged in seconds (7.1%), minutes to 2 hour (31%), 2~24 hours (13.1%), and >24 hours (48.8%). Besides, only 5 patients (5.5%) reported a consistent temporal pattern of dizziness in relation to migraine. Another series by Dieterich and Brandt (1999) had also noted a wide range of vertigo duration, ranging from seconds to days. In the contrary, 68% of patients recalled headache attacks associated with vertigo episodes. Recently, Neuhauser et al. (2001) emphasized the “migrainous symptoms”, which can also be noted during vertiginous attack, including photophobia (70%), phonophobia (64%) and visual auras (36%). Furthermore, he pointed out that 94% of the patients had association between migrainous headache and vertiginous episode.

In summary, clinical manifestation of migraine-related vertigo had enclosed the following features. Demographically, young to middle-aged women are most susceptible to this disease with a strong familial preponderance. Symptomatically, vestibular symptoms may occur not only during headache but also in headache-free

intervals, presented as motion intolerance. Etiologically, precipitants of migraine may induce vestibular episodes with a wide range of severity and duration of attacks. In addition, some of these subjects may also notice the presence of photophobia, phonophobia and scintillating scotoma during vertigo attacks.

2.2 Objective assessment

Except for the subjective symptoms, objective audiovestibular function testing had also been applied, including audiometry, caloric test with electronystagmographic (ENG) recordings. Kayan and Hood (1984) examined 80 patients of migraine and disclosed an overall 78% (62/80) of cochleovestibular abnormalities, including 11 abnormal optokinetic nystagmus (OKN) test, 51 abnormal caloric test (canal paresis and/or directional preponderance), and 22 abnormal hearing test. He concluded that 15 patients were referred to central lesions, 23 patients with peripheral lesions, while 24 patients remained inconclusive. These higher than expected abnormal rates could be attributed to the selection bias, since all patients in this series were referred from other facilities.

Another case series conducted by Cutrer and Baloh (1992) had similar neurotological findings. In the 91 patients recruited, spontaneous nystagmus was observed in 6 patients, positional nystagmus 6, canal paresis 19 and directional

preponderances 7, constituting overall 34% abnormalities on ENG tests. However, results of audiometry were not reported in this study. Likewise, Cass et al. (1997) reviewed 100 patients of "migraine-related vestibulopathy" and 39% of them showed abnormalities on ENG, including 22 canal paresis, 3 abnormal pursuit tests, and 2 abnormal OKN tests. Hearing was normal in 80 out of 89 patients who underwent audiometry. Additionally, Dieterich and Brandt (1999) retrospectively reviewed the neurotological results over the disease free interval in 90 patients with "vestibular migraines". They depicted 66% of patients with central lesions on ENG testing, and saccadic pursuit being the most frequent one (70%), followed by gaze-evoked nystagmus (27%). Notably, these results were mainly recorded during the symptom-free intervals. It was until von Brevern et al. (2005) that information on acute attack had been investigated. In this prospective study of 20 acute migrainous vertigo, 4 patients with abnormal audiogram was noted but remained unchanged after episode subsided, with presbycusis being the most likely diagnosis. Fourteen pathological nystagmus were no longer recorded after acute attacks. In brief, central lesion accounts for 50% of acute migrainous vertigo, while peripheral lesions in 15% and the other 35% remained inconclusive.

Thus, objective assessment of migraine-related vertigo and dizziness had mainly based on neurotological testing. Pathological nystagmus may occur during

attacks, but be absent in most cases during the disease-free interval. ENG abnormalities are observed in either acute episodes or symptom free period, with 40-60% abnormalities in OKN, pursuit or saccade tests. As regard to caloric test, it may demonstrate canal paresis in 20-30%, indicating a lesser extent of peripheral involvement of vestibular symptoms. In contrast, audiometry remains normal in most cases, at least unchanged before and after acute episode. Once hearing loss is present, it is attributable to primary presbycusis or other underlying etiologies.

2.3 Pathophysiology

Subsequent studies of migraine-related vertigo had focused on the spectrum of clinical manifestations and investigated the underlying pathophysiology. Earlier studies prefer the mechanism of prolonged vasoconstriction with resultant dysfunction of audiovestibular system (Kuritzky et al., 1981; Kayan and Hood, 1984). There were three mechanisms proposed according to different phases of headache, i.e.: vasoconstriction of basilar and vertebral artery in pre-headache phase; prolonged vasoconstriction during headache; and aura without headache (migraine equivalent) in headache-free periods. However, vasoconstriction as the sole mechanism of migraine-related vertigo had been challenged by the ongoing understandings of the complex neuronal pathways and various active

neurotransmitters during migraine attack.

Currently, pathophysiological models of migraine (Goadsby, et al., 2002) had incorporated the following components: 1) neuroactive peptide, e.g. serotonin and norepinephrine; 2) trigeminal parasympathetic reflex; 3) vasoactive agents and subsequent sterile inflammation around dura; and 4) spreading wave of depression. Although migrainous vertigo was less well understood than migraine itself, vertigo has no longer been regarded as simply an aura symptom of migraine. Cutrer and Baloh (1992) proposed that transient vasospasm and spreading wave of depression was the underlying mechanism for shorter duration of vertigo (<2 hours), which corresponded to the typical aura of migraine. Nevertheless, for longer duration of dizziness, release of neuroactive peptide and the subsequent increased baseline firing of efferent fibers explained dizziness and the associated hypersensitivity to motion. Likewise, Cass et al. (1997) suggested that asymmetric activation and deactivation of vestibular neuronal activity through serotonergic and peptidergic pathways resulted in vestibular tone imbalance, which could account for oculomotor deficit and subsequent vertigo attack (Dieterich and Brandt, 1999).

Up to date, the most comprehensive review by Furman et al. (2003) had pointed out three likely models for the pathogenesis of migraine-related vertigo. The first one is through central connections including dorsal raphe nucleus, locus

ceruleus, trigeminal and vestibular nuclei. Causative agents of migraine are likely to induce vestibular symptoms through these central neuronal connections. The second one is inner ear dysfunction through neuropeptide release, e.g. substance P, calcitonin gene-related peptide and neurokinin A, from trigeminal and audiovestibular nerve fibers. Thirdly, short-duration vestibular symptoms could be contributed to vasospasm and resultant ischemia, especially for those with abnormalities of calcium-channel gene on chromosome 19p, as documented in cases of familial hemiplegic migraine (Baloh, et al., 1997). Besides, an autosomal dominant fashion of inheritance with decreased penetrance in male subjects was suggested, partly explained the predominance of female patients (Oh, et al., 2001).

2.4 Nomenclature and diagnostic criteria

The most recognized operative diagnostic criteria for basilar artery migraine was first proposed by the IHS, 1st edition, 1998, which requires migrainous headache, coupled with two or more preceding "aura" symptoms from posterior circulation, i.e. dysarthria, tinnitus, hypacusia, diplopia, visual symptoms, ataxia, decreased consciousness and bilateral paresthesia. These aura symptoms must last for 5 to 60 minutes and followed by migrainous headache within 60 minutes. As a result of the strict definition, most of the vestibular symptoms fail to present as an

"aura" symptom (Kayan and Hood, 1984), and less than 10% of clinically suspected patients of migraine-related vertigo fulfilled this criteria (Dieterich and Brandt, 1999; Neuhauser et al., 2001).

Therefore, various diagnostic criteria and corresponding nomenclature had been postulated, despite the IHS guidance. The summary of each criterion was given in Appendix I. Among those proposed criteria, definite and probable migrainous vertigo proposed by Neuhauser et al. (2001) was by far the most widely accepted one. To diagnose "definite migrainous vertigo", it requires recurrent vestibular symptoms of at least moderate severity, migraine according to IHS criteria, temporal association between migrainous symptoms and vertigo, and exclusion of other causes. Similarly, to diagnose "probable migrainous vertigo" requires either migraine, migrainous symptoms during vertigo attacks, migraine precipitant, or response to migraine medications, plus vestibular symptoms but excluding other causes as well. Even though this criterion had received great attention, universal consensus was not yet established. Brantberg et al. (2005) conducted a structured interview of 40 patients and 40 symptom-free relatives and argued that temporal association was experienced in less than half of the patients. Meanwhile, photophobia, phonophobia and scintillating scotoma were too ambiguous for diagnosis. He disputed that neither temporal sequence between migraine and vertigo

nor migrainous symptoms during vertigo attack should be included in the diagnostic criteria.

Despite lack of gold standard to diagnose migraine-related vertigo and dizziness, several agreements had been achieved so far. First, personal history of migrainous headache (by IHS criteria) should be present; second, recurrent vestibular symptoms should be present; and third, other vestibular disorders, e.g. Meniere's disease, vestibular neuritis and benign paroxysmal positional vertigo should be excluded. Meanwhile, the major debate remains in the following categories: 1) temporal sequence between vertigo and migraine; 2) duration and other characteristics of vertigo attack; 3) migraine precipitant; 4) family history and 5) inclusion of audiovestibular function tests.

2.5 Therapeutic options and studies of treatment effectiveness

Modern management for migrainous headache composed mainly two distinct purposes: drugs for acute attacks and for prophylaxis. The former consists of triptans, ergot alkaloid, NSAIDs, antiemetics and combinations such as acetaminophen plus aspirin and caffeine (Silberstein, 2000). For the prophylactic treatment, the indications include frequent headache significantly interfering daily routines, adverse effects with acute therapies, presence of basilar migraine…etc. Recommended regimens include beta-blocker, anti-epileptic, anti-depressant and

SSRI. Although not FDA-approved in U.S., calcium channel blocker, e.g. flunarizine, had been widely prescribed in the Europe for migraine prophylaxis (Evers, et al. 2006). Although not yet clear, possible mechanisms are inhibition of vasospasm induced by mediators such as serotonin and prostaglandins, inhibition of cellular hypoxia, improved blood viscosity and erythrocyte deformability.

Despite less study on the treatment of migraine-related vertigo, earlier literature had already suggested trial of anti-migraine medication in patients with benign recurrent vertigo (Slater 1979). Several published series also demonstrated that migraine prophylactic medication was effective in migraine-associated vestibular disorders (Dieterich and Brandt, 1999), and most of the subjects experienced equal reduction of both migraine and vertigo (Bikhazi, et al., 1997), even in subjects without active headache (Reploeg and Goebel, 2002).

The primary outcome measurement among these studies was based on subjectively ratings for the effectiveness of treatment. For example, Johnson (1998) used mainly chart reviews with additional telephone contact and mailed questionnaire in case of inadequate chart records or lost follow-ups. Assessment of treatment outcome was divided into 5 categories: complete resolution, substantial resolution, moderate control, partial control and no improvement. Maione (2006) had conducted another prospective observational study in 53 patients, using a similar

outcome category via self-report questionnaires. Another study measured reduction of attack frequency to determine the effectiveness of management (Reploeg, 2002). The prophylactic medications used in these studies consisted beta- blocker, calcium channel blocker and antidepressant in most cases. Although these studies all demonstrated good response, various treatment modalities and different prescribed medications had made the comparison between them quite difficult.

3. Objectives

The goals of this study composed three parts. First, to present the clinical manifestations of migraine-related vertigo and dizziness. Since the published series consisted mainly Caucasians, this study aimed to collect a more representative sample of Asian (Taiwanese). By comparing our results with the literatures, the difference between ethics can be explored and this information will be beneficial in the clinical practice and future academic research.

Second, to explore the association between clinical characteristics and treatment effectiveness. The complex disease spectrum and various clinical presentations had lead to difficulties in the consensus of diagnostic criteria. However, since the clinical diagnosis of migraine-related vertigo and dizziness had mainly relied on personal history of migraine with excluding other possible causes, debating which specific characteristic was a diagnostic requirement is trivial. In stead, by identifying the significant factors in relation to treatment effectiveness, we may tailor the clinical management individually, and offer more relevant information upon patient counseling.

Third, to investigate the relationship between different diagnostic groups. Although a variety of diagnostic criteria has been proposed, no study had performed a comparison between them. In other words, the relationship between these

diagnostic groups remained unclear, not to mention its correlation with treatment effectiveness. Therefore, via classifying our study population by different diagnostic criteria, namely basilar type migraine, definite and probable migrainous vertigo, the clinical manifestation and treatment effectiveness were investigated.

4. Subjects and Methods

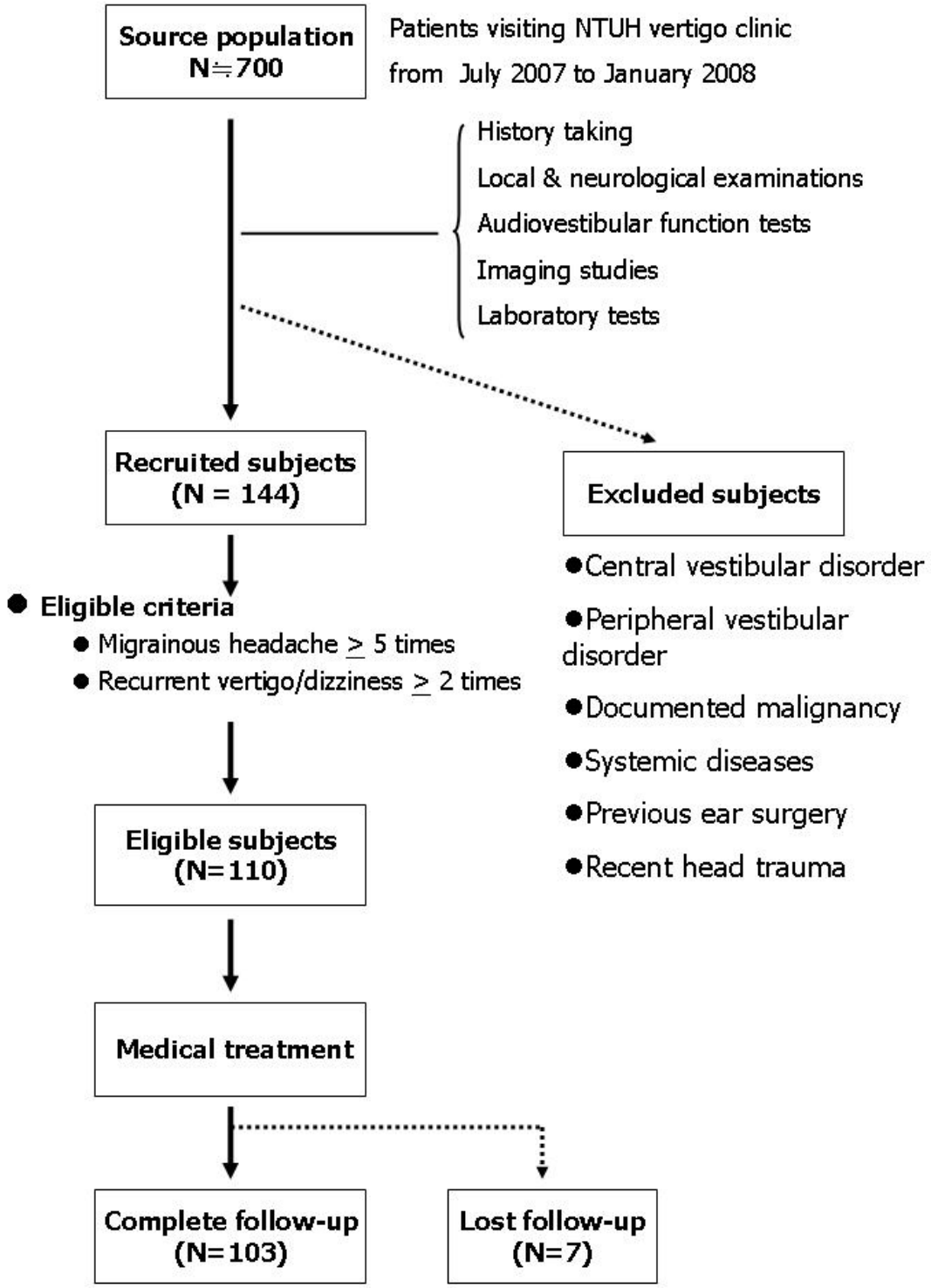
4.1 Study design and enrollment of subjects

The source population was comprised of patients visiting vertigo special clinic of National Taiwan University Hospital (NTUH) from July 2007 to January 2008, approximately 700 patients. All the subjects underwent a battery of tests including local check-up of the ear, nose and throat fields, neurological examination, blood chemistry profile, plain radiographic examination for mastoid and internal acoustic canal, audiometry and electronystagmographic (ENG) examination. Once the clinical diagnosis was established, subjects with either peripheral vestibular disorders, e.g. benign paroxysmal positional vertigo (BPPV), Meniere's disease, vestibular neuritis, or central vestibular disorders such as vertebrobasilar insufficiency (VBI), vestibular schwannoma and stroke, etc. were all excluded from this study. Besides, those with systemic disease, such as anemia, syphilis or hyperlipidemia, which account for the clinical symptoms, were excluded as well. Other exclusion criteria included previous ear surgery, documented malignancy and recent head trauma (within 6 months).

Subsequently, subjects with at least five attacks of migrainous headache and more than 2 episodes of vertigo or dizziness were enrolled. Migrainous headache consisted of migraine with aura, migraine without aura and probable migraine,

according to the (IHS) criteria, 2nd edition (2004). Those with tension, cluster and other undetermined patterns of headache were excluded. Finally, 110 subjects were eligible and composed the study population. Each subject was treated with a consecutive 3-month medication including flunarizine, 10mg, once daily; oxazolam, 10 mg, twice daily, plus multiple vitamins daily. All patients were regularly followed up at our clinic monthly to evaluate the improvement of corresponding symptoms. Figure 1 illustrates the flow chart of study design and enrollment of subjects.

Figure 1. Flow chart of study design and enrollment of subjects



4.2 Data collection and definition of variables

All the clinical information was collected by the author via face-to-face, structured interviews (Appendix II). The purpose of the study was explained to each patient and informed consent was signed prior to the interview and the recording of laboratory results (Appendix III). The analyzed headache and vertigo characteristics included frequency, severity and duration of attacks. A detailed family pedigree was plotted up to second-degree relatives and subjects were asked to recall if any of these family members had headache attacks. A positive family history was defined as one or more probands being affected. Initial presenting symptoms (headache and/or vertigo), age at onset, and the duration of history were recorded. Age at onset were recorded by a 10- year span, i.e. 0~9, 10~19, 20~29, 30~39 and >40 years old. The presence of common and specific auras, e.g. dysarthria, tinnitus, hypacusia, diplopia, visual symptoms, ataxia, decreased consciousness, and bilateral paresthesia were investigated. Motion sickness was recorded on a life-time basis. Migraine precipitants such as stress, sleep irregularity, menstruation period and food were recorded. The latter consisted of dairy products, milk tea, tangerine, grapefruit, chocolate, wine, iced drinks and tomato. The information of food precipitation was collected by self-filling inquiry as shown in Appendix IV. Positive precipitation regards association in more than half of the attacks of headache or vertigo, which

was explained to the patient before filling out the inquiry form.

The treatment effectiveness was investigated by chart review after all the patients had completed the treatment course. Subjective improvement of headache and vestibular symptom was evaluated separately. Of the 17 subjects who failed to visit the clinic regularly, 10 were successfully contacted through telephone calls, while the remaining 7 patients were lost despite repeated telephone contacts. The treatment effectiveness was scored as: 0 point: subsidence of the symptoms; 1 point: occasional attack but improved; 2 points: persistent symptoms or worse. Composite scores by summing points for headache and vertigo had constituted the final treatment effectiveness, namely:

0 point: complete resolution;

1 point: substantial control;

2 points: moderate control;

3 points: partial control;

4 points: unchanged

Good response is defined as 0-1 point, while 2 to 4 points refers to poor response.

4.3 Audiovestibular function tests

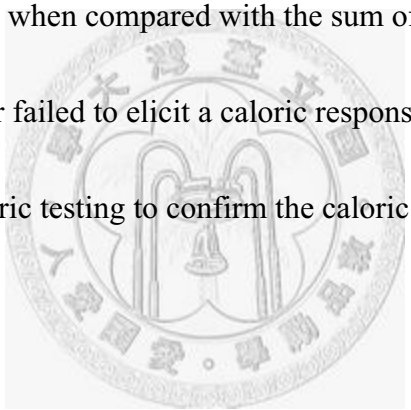
Audiovestibular function tests include audiometry and ENG examination. Of the audiometry, abnormal hearing is defined when the pure tone average of 500, 1000 and 2000Hz exceeds 25dB. ENG (OK-5, Nagashima, Tokyo, Japan) examinations consisted of recording the spontaneous nystagmus first, followed by eyes tracking (pursuit and saccade), optokinetic nystagmus (OKN) and caloric tests.

The pursuit test was performed in seated position with the subject's head mechanically fixed and asked to follow a moving target at a distance of 100 cm moving in a clockwise circle, with a radius of 25.5 cm at a constant rate of 120°/s. The horizontal component of the eye movement was represented in a sinusoidal curve of 0.33 Hz with a maximum displacement of 20° from the center. Subsequently, saccade test was performed by asking the subject to followed a quick moving target separated by 30°within 2 s. During these tests, abnormal results constituted saccadic pursuit, ataxic pursuit, dysmetria, overshoot and undershoot of the saccade test.

The OKN test was triggered by a horizontal optokinetic stimulation with an angular velocity from 0 to 140°/s at an angular acceleration of $+4°/s^2$, then from 140 to 0°/s at an angular acceleration of $-4°/s^2$, by using a revised Jung-type Ohm-drum for stimulation. During these tests, overshooting of OKN, loss of laterality, or

inversion of bilateral OKN was defined as abnormal. Loss of laterality in OKN tests indicates that information on laterality is lacking, which can be strongly affected by lesion in central vestibular nucleus. In contrast, inversion of bilateral OKN implies congenital nystagmus.

Cold-water caloric test was performed using 20 ml tap water irrigating the external ear canal for 20 s with ENG recordings. Canal paresis was defined as a greater than 25% difference between the maximum slow phase velocity measurements for each ear, when compared with the sum of slow phase velocities from each ear. If cold water failed to elicit a caloric response, the subject underwent ice water (0^{o}C, 10mL) caloric testing to confirm the caloric areflexia.



4.4 Diagnostic and classification criteria

The study population was classified into three groups that are basilar type migraine (BtM), definite migrainous vertigo (dMV) and probable migrainous vertigo (pMV) according to the diagnostic criteria (Table 1). Only subject with true rotatory vertigo were considered “recurrent vestibular symptoms of at least moderate severity” in the first diagnostic requirement of both dMV and pMV. Notably, these criteria had a trend of hierarchy, which means that subjects fulfill BtM will mostly fulfill dMV, and subjects fulfill dMV inevitably fulfill pMV. Therefore, diagnostic priority is BtM first, followed by dMV, while pMV being the last one. Totally 77 out of 110 patients could be classified, including BtM in 15 patients, dMV in 30 patients and pMV in 32 patients. The remaining 33 subjects who failed to fulfill any of the above diagnostic criteria were labeled as “unclassified”.

Table 1. Diagnostic criteria of basilar type migraine, definite and probable migrainous vertigo

Basilar type migraine	Definite migrainous vertigo	Probable migrainous vertigo
1. At least two attacks fulfilling criteria 2-4	1. Episodic vestibular symptoms of at least moderate severity	1. Episodic vestibular symptoms of at least moderate severity
2. At least two fully reversible aura symptoms*	2. Migraine according to the IHS criteria	2. At least one of the following features[+]
3. Duration of aura symptoms lasted ≥ 5 and ≤ 60 min	3. At least one of the migrainous symptoms during at least two vertiginous attacks[#]	3. Other causes ruled out by appropriate investigations
4. Migrainous headache begins during the aura or follows within 60 min	4. Other causes ruled out by appropriate investigations	
5. Not attributed to other disorder		

*: Dysarthria, tinnitus, hypacusia, diplopia, visual symptom, ataxia, decreased consciousness and bilateral paresthesia

[#]: Migrainous headache, photophobia, phonophobia, visual or other auras

[+]: migraine according to the criteria of the IHS; migrainous symptoms during vertigo; response to anti-migraine drugs; migraine-specific precipitants of vertigo, e.g., specific foods, sleep irregularities, hormonal change

4.5 Result analysis and statistical methods

Result analysis was divided into three parts: clinical manifestation, its correlation with treatment effectiveness, and the comparison between three diagnostic groups. First, a descriptive study of eligible subjects regarding demographics and clinical manifestations was conducted. Second, univariate analysis of each clinical characteristic and its correlation with treatment outcome were evaluated. Since the outcome was coded in ordinal scale (0 to 4 point), non-parametric methods were applied including Cochran-Armitage trend test (ordinal vs. binomial; for example: gender), Kruskal-Wallis test (ordinal vs. categorical; for example: type of headache), and Kendall's Tau test (ordinal vs. ordinal; for example: frequency of symptoms). Age was treated as continuous variable and its relationship with outcome was investigated by cumulative logits model. In case of gross association but non-significant statistical result (mostly due to scarce cell numbers), outcome were regarded as dichotomous variable (good vs. poor response) and its correlation with clinical factors was re-evaluated using chi-square test with correction of continuity. Factors with p-value less than 0.1 in the univariate analyses warranted subsequent multivariate analysis. Cumulative logits regression was applied in the multivariate analysis, regarding treatment effectiveness as ordinal scale (0-4 points). If the proportional odds assumption can not be fulfilled, logistic regression was applied alternatively using

dichotomous treatment response (good vs. poor). Standardized Pearson residual was checked in each subject to look for potential outlier (greater than 2 standard deviations), which was then excluded in the final modeling.

Thirdly, comparative analysis of the three diagnostic groups, i.e. BtM, dMV and pMV, was conducted to evaluate the relationship between them. Unclassified subjects were excluded in this section. For continuous data such as age at onset, age at presentation, one-way analysis of variance (ANOVA) was used to test differences between three groups. For dichotomous variables, e.g. presentation of specific symptoms and abnormalities of audiovestibular function tests, Chi-square test or Fisher's exact test was performed. For ordinal variables, Cochrane-Armitage trend test, Kruskal-Wallis test or Kendall's Tau test were applied. In addition, polytomous logistic regression was used for multivariate analysis.

All statistical analyses were conducted by SAS software, version 9.1 (SAS Institute, Inc. Cary, North Carolina, U.S.) and SPSS software, version 13.0 (SPSS Inc. Chicago, Illinois, U.S.).

5. Results

5.1 Descriptive analysis of clinical manifestation

5.1.1 Demographics

One-hundred and ten subjects were enrolled and eligible for the study, including 93 female (85%) and 17(15%) male patients. The mean age at presentation was 40 ± 13 years (mean ± SD) and the detailed distribution of age at onset of symptoms was illustrated in Figure 2, with the majority lies between 10 to 29 years old. Meanwhile, 67 subjects (61%) reported headache as their first presenting symptoms (Table 2). Additionally, 79 (72%) of our subjects had positive family history (Table 2).

Figure 2. Age at onset of symptom

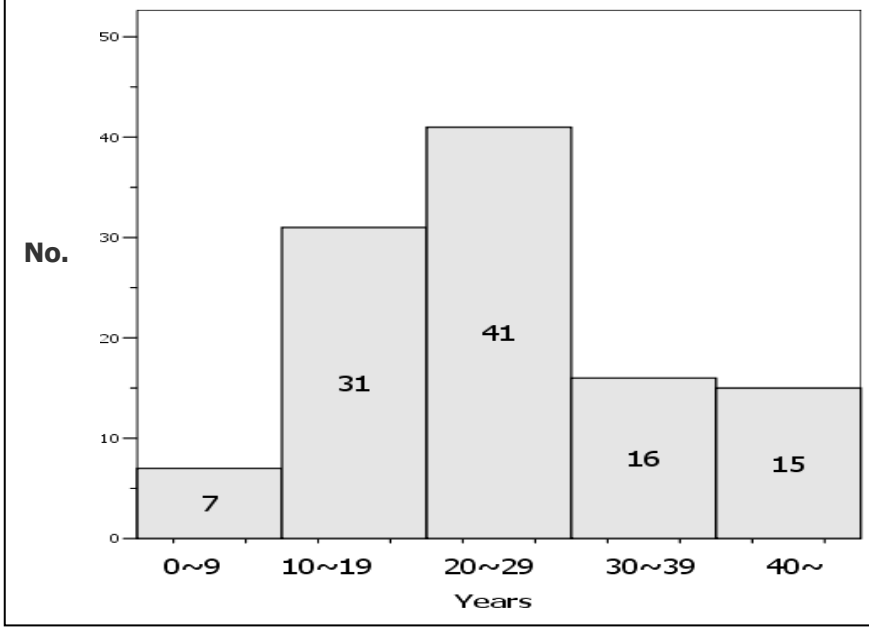


Table 2. Demographics of 110 eligible subjects

Factors	Occurrence rate
Gender	
Male	17 (15%)
Female	93 (85%)
First presenting symptoms	
Headache	67 (61%)
Vertigo/dizziness	21 (19%)
Both	22 (20%)
Family History	
Positive	79 (72%)
Negative	31 (28%)

5.1.2 Characteristics of vestibular symptoms

The distribution of attack frequency was widely distributed, ranging from less than 5 times to more than once per week (Table 3). Similarly, the duration of vestibular symptoms was also quite variable, as demonstrated in Table 3. Seventy-four patients (67%) suffered from true rotatory vertigo while the rest complained of non-rotatory dizziness. Fifty-four subjects (49%) experienced a sequential relationship between migraine and vestibular symptoms, including simultaneous attack in 20, migraine preceded vertigo/dizziness in 21, and vertigo/dizziness preceded migraine in 13, while more than half (51%) of the subjects denied any sequential relationship at all (Table 3). Regarding the migrainous symptoms during vestibular episodes, phonophobia was the most common recognized one, accounting for 64 subjects (58%), followed by photophobia in 45 (41%) and scintillating scotoma in 30 (27%). Overall, nearly two thirds (64%) of the subjects had at least one of the above migrainous symptoms during vestibular episodes. Additionally, 75 patients (69%) had suffered from motion sickness on a lifetime basis.

Table 3. Characteristics of vestibular symptoms in 110 patients

Factors	Occurrence rate
Frequency	
<5 times / < 1/year / <1 /month / <1/wk / ≥ 1/wk	16 / 6 / 35 / 30 / 23
Duration	
Seconds / Minutes / Hours/ Days	32 / 36 / 25 / 17
Subjective sensation	
Rotatory	74 (67%)
Non-rotatory	36 (33%)
Sequential relationship	
Simultaneous	20 (18%)
Migraine precede vertigo/dizziness	21 (19%)
Vertigo/dizziness precede migraine	13 (11%)
Denied	56 (51%)
Migrainous symptoms	
Phonophobia	64 (58%)
Photophobia	45 (41%)
Scintillating scotoma	30 (27%)
At least one of above	70 (64%)
Motion sickness	
Present	75 (69%)
Absent	35 (31%)

5.1.3 Characteristics of migrainous headache

The headache patterns were classified based on the IHS criteria (2nd edition, 2004), including migraine without aura in 71 subjects, migraine with aura in 16, and probable migraine in 23 (Table 4). The most frequent aura symptoms referred to tinnitus and bilateral paresthesia, both constitute for 11 patients (69%). Probable migraine consisted of subjects fulfilling all but one criterion in the diagnosis of migraine without aura. Nearly half (48%) of the subjects had migraine attacks less than once per month, while the rest had more frequent attacks (Table 4). The most common precipitating factor of migraine was sleep irregularity, consisting 78 subjects (71%). Seventy-two subjects (65%) had their migraine attacks related to stress. Almost half of the subjects recalled a precipitation with specific food. Dairy products and milk tea were the most common food precipitants, accounting for 21 subjects (19%) and 19 subjects (17%), respectively. Among 85 female subjects with active menstruation cycle, 49% (42/85) had their headache attacks related to the menstruation period, and most of them mentioned the symptom attacks prior to the menstruation period. In summary, up to 106 subjects (96%) had at least one of these migraine precipitants.

Table 4. Characteristics of headache

Factors	Occurrence rate
Classification	
Migraine without aura	71 (64%)
Migraine with aura*	16 (15%)
Probable migraine	23 (21%)
Frequency of headache	
< 1/year	1 (1%)
< 1/month	51 (47%)
<1/week	29 (26%)
≥1/wk	29 (26%)
Precipitants	
Sleep irregularity	78 (71%)
Stress	72 (65%)
Food	54 (49%)
Menstruation related (N=85)[#]	42 (49%)
Pre- / During- /Post-menstruation	33 / 9 / 0

*: Include basilar type migraine (BtM)

[#]: Female subjects with active menstruation cycle

5.1.4 Audiovestibular function tests

In the current study, most subjects revealed normal hearing with only 2 patients (2%) showed abnormal hearing (Table 5). Twenty-three patients (21%) showed abnormalities of caloric test, including canal paresis in 14 subjects, dysmetria in 3, areflexia in 4, and loss of visual suppression in 2. ENG examinations demonstrated abnormal OKN test in 41%, spontaneous nystagmus in 28%, abnormal pursuit and saccade test in 22% and 17%, respectively.

Table 5. Audiovestibular function tests

Tests	**Abnormal rate**
Audiometry	2 (2%)
Caloric tests	23 (21%)
Electronystagmography	
Optokinetic nystagmus	45 (41%)
Spontaneous nystagmus	31 (28%)
Pursuit test	24 (22%)
Saccade test	19 (17%)

5.2 Correlation between clinical manifestations and treatment effectiveness

Excluding 7 patients lost from the clinic, 103 subjects with reliable treatment effectiveness were investigated. The result demonstrated complete resolution in 49 patients (48%), substantial control in 25 (24%), moderate control in 15, partial control in 7, and unchanged in 7 (Table 6), corresponding to 74 patients (72%) of good response (complete resolution and substantial control), and 29 subjects (28%) of poor response of treatment (moderate control, partial control and unchanged).

Table 6. Treatment effectiveness

Outcome	Number of patients
Good response	**74 (72%)**
Complete resolution	49 (48%)
Substantial control	25 (24%)
Poor response	**29 (28%)**
Moderate control	15 (14%)
Partial control	7 (7%)
Unchanged	7 (7%)

5.2.1 Univariate analysis

All the clinical and laboratorial factors were analyzed for its correlation with treatment effectiveness, in order to identify factors with p value less than 0.1 for further multivariate analysis. Regarding the demographic factors, age at presentation was correlated with treatment effectiveness (p=0.05, cumulative logits regression, β=0.027), comparing with a less association with age at onset of symptoms (p=0.08, Kendall's Tau test), which indicated that younger subjects presented with poorer response of medication. On the contrary, gender and the presence of familial history fail to show such correlation, either.

The analysis of vestibular symptoms demonstrated that patients suffered from more frequent vestibular episodes tended to have poorer outcome, compared to those with less attacks (p=0.08, Kendall's Tau-b = 0.20). On the contrary, duration of vestibular symptoms only showed a minimal correlation with outcome (p=0.08, Kendall's Tau-c coefficient = -0.06). Regarding the association between treatment effectiveness and other characteristics of vertigo and dizziness, i.e. subjective sensation (rotatory vs. non-rotatory), migrainous symptoms during vestibular episodes, sequential relationship between headache and vertigo, and presence of motion sickness , none of these factors showed correlations with treatment effectiveness (Table 7).

Table 7. Treatment effectiveness vs. vestibular symptoms

Factor	Number of patients					p-value*
	CR	SC	MC	PC	UC	
Subjective sensation						0.53
Rotatory	35	15	9	7	3	
Non-rotatory	14	10	6	0	4	
Migrainous symptoms						0.25
Present	34	19	8	4	4	
Absent	15	6	7	3	3	
Motion sickness						0.10
Present	32	15	10	7	6	
Absent	17	10	5	0	1	
Sequential relationship						0.23
Related	31	11	5	2	5	
Unrelated	18	14	10	5	2	

*: Cochrane-Armitage trend tests

CR: Complete resolution

SC: Substantial control

MC: Moderate control

PC: Partial control

UC: Unchanged

The correlation between characteristics of headache and treatment effectiveness was investigated subsequently. First, although the association between treatment effectiveness and subtypes of headache (migraine with aura, migraine without aura and probable migraine) were non-significant (Table 8, p=0.12, Kruskal-Wallis test, degree of freedom=2), comparing migraine with aura to the combination of the other two types revealed a stronger correlation with worse outcome (p=0.05, Cochrane-Armitage trend test). Similarly, frequency of headache attacks also showed some correlation with poorer outcome (Table 8. p=0.08, Kendall's Tau-c = 0.13). Considering common precipitants of migraine, i.e. sleep, stress, menstruation period and food, the latter was the only one with potential correlation with treatment effectiveness (Table 8, p=0.06, Cochrane-Armitage trend test). Notably, precipitation by menstruation period was only recorded among 85 female subjects with active menstruation cycle.

Except the 5-category treatment effectiveness, all the factors with a p value more than 0.1 in Table 7 and 8 had also received additional investigation of the association with binomial treatment effectiveness, i.e. good vs. poor response. None of these factors had demonstrated a p value of less than 0.1 and hence had all been excluded from the subsequent multivariate analysis.

Table 8. Treatment effectiveness vs. characteristics of headache

Factors	Number of patients					p value
	CR	SC	MC	PC	UC	
Subtype of headache						0.12[+]
Migraine with aura	5	3	4	2	2	
Migraine without aura	34	16	10	3	2	
Probable migraine	10	6	1	2	3	
Frequency of headache						0.08[#]
< 1/year	0	1	0	0	0	
< 1/month	28	6	7	1	3	
<1/week	9	10	5	3	1	
≥1/wk	12	8	3	3	3	
Sleep irregularities						0.68*
Present	34	21	12	5	5	
Absent	15	4	3	2	2	
Stress						0.82*
Present	31	16	11	5	4	
Absent	18	9	4	2	3	
Menstruation						1*
Present	20	9	7	2	3	
Absent	20	12	6	4	2	
Food						0.06*
Present	31	9	5	3	3	
Absent	18	16	10	4	4	

[+]: Kruskal-Wallis test

[#]: Kendall's Tau-c = 0.13

*: Cochrane-Armitage trend test

Considering all the audiovestibular function tests used in this study, none of them showed significant association with the treatment outcome, including caloric test, spontaneous nystagmus, pursuit, saccade and OKN tests (Table 9, $p \geq 0.10$, Cochrane-Armitage trend test). Nevertheless, re-examining the association between OKN tests and dichotomous treatment response (good vs. poor), it demonstrated that 50 out of 61 subjects (82%) with normal OKN results showed good responses. In contrast, among subjects with abnormal OKN results, only 57% (24/42) had good responses ($p=0.01$, Chi-Square test with correction of continuity). However, evaluate the other audiovestibular function tests with dichotomous treatment response did not reveal such correlation as well.

Table 9. Audiovestibular function tests vs. treatment effectiveness

Factors	Number of patients					p value*
	CR	SC	MC	PC	UC	
Caloric test						0.10
Normal	35	22	13	5	7	
Abnormal	14	3	2	2	0	
Pursuit test						0.66
Normal	39	20	9	6	7	
Abnormal	10	5	6	1	0	
Saccade test						0.50
Normal	41	20	10	7	7	
Abnormal	8	5	5	0	0	
Spontaneous nystagmus						0.19
Presence	15	8	4	2	0	
Absence	34	17	11	5	7	
Optokinetic nystagmus						0.21
Normal	32	18	2	4	5	
Abnormal	17	7	13	3	2	

*: Cochrane-Armitage trend test

5.2.2 Multivariate analysis

Factors with p value less than 0.1 in the univariate analyses were entered in the subsequent multivariate analysis. Gender was adjusted in the model despite its non-significant correlation with outcome. In addition, the strength of correlation in the "duration of vestibular symptoms" was so small (Kendall's Tau-c = -0.06) that it was excluded from the multivariate analysis. Furthermore, since frequency of vertigo and headache attacks were correlated with each other (Kendall's Tau-c = 0.14), in order to prevent co-linearity, only frequency of vestibular symptoms was remained considering its higher association with treatment effectiveness. Similarly, age at onset was excluded because of its high correlation with age at presentation. As a result, totally six variables, i.e. age at presentation, gender, frequency of vertigo, subtype of headache, food precipitation, and OKN test were applied in the final multivariate analysis. Frequency of vertigo and subtype of headache were further transformed dichotomously for better clinical application and interpretation. Frequency of vertigo was recoded by combining those with attack frequency $\geq$ 1/month into one group, while the rest into the other. In addition, since subjects of migraine with aura had poorer treatment response, the other two types of headache, i.e. migraine without aura and probable migraine, were grouped together. After excluding 3 outliers with Pearson residuals greater than 2 standard deviations, totally

100 subjects were included in the final analysis.

The result was summarized in Table 10, including adjusted odds ratio (aOR), 95% confidence interval (CI) and the corresponding p value. Age at presentation, frequency of vestibular symptoms, and OKN test were significantly associated with outcome after adjusting for other factors. Subjects with each 10-year decline of age had a 2.38-fold risk of having poor response of treatment ($p<0.01$, 95% CI: 1.39 ~ 4.07). Patients with vestibular episodes ≥ 1/month tend to have poorer outcome than those with less frequent attacks ($p<0.01$, aOR=7.73, 95% CI: 2.05 ~ 19.1). Similarly, abnormal OKN results were significantly correlated with worse outcome ($p<0.01$, aOR=5.40, 95% CI: 1.60 ~ 18.2). Food precipitation demonstrated a borderline significance, indicating that subjects with symptom episodes precipitated by food tend to have better response of medication ($p=0.06$, aOR=0.31, 95% CI: 0.09~ 1.04). Subtypes of headache, despite its significant correlation in the univariate analysis, fail to reach significance when controlling for other factors. Finally, examining the goodness-of-fit in this multiple logistic regression model had revealed an acceptable result with c-value equal to 0.88.

Table 10. Multivariate analyses of treatment effectiveness (N=100)

Factors	aOR*	95% Confidence Interval	p value
Age at presentation (each 10 year decline)	2.38	1.39 ~ 4.07	**<0.01**
Frequency of vestibular symptoms (≥ 1/month vs. less)	7.73	2.05 ~ 19.1	**<0.01**
OKN test (abnormal vs. normal)	5.40	1.60 ~ 18.2	**<0.01**
Food precipitation (present vs. absent)	0.31	0.09 ~ 1.04	0.06
Subtype of headache (migraine with aura vs. other types)	3.08	0.79 ~ 12.0	0.11
Gender (female vs. male)	3.26	0.50 ~ 21.3	0.22

*: Adjusted odds ratio

5.3 Comparison between different diagnostic groups

5.3.1 Demographics

Further comparison were conducted for those fulfill either of the three diagnostic criteria, namely basilar type migraine (BtM), definite migrainous vertigo (dMV) and probable migrainous vertigo (pMV). Totally 77 patients were analyzed, including BtM in 15, dMV in 30 and pMV in 32. The age at presentation was 40 ± 14 (mean ± SD) years in the BtM group, 41 ± 13 years in the dMV group and 43 ± 12 years in the pMV group, exhibiting non-significant difference (Table11, p=0.70, one-way ANOVA test). The distribution of gender and the presence of family preponderance were similar between three groups. Additionally, onset of symptom did not differ significantly, either (p=0.33, Kruskal-Wallis test, degree of freedom=2).

Table 11. Demographics of three diagnostic groups

Factors	**BtM**	**dMV**	**pMV**	**p value**
Case number	15	30	32	
Age (years, mean ± SD)	40± 14	41 ± 13	43 ± 12	0.70*
Gender (M / F)	2 / 13	2 / 28	3 / 29	0.78^{+}
Family history (presence / absence)	4 / 11	7 / 23	11 / 21	0.62$^{\&}$

*: One-way Analysis of Variance (ANOVA)

$^{+}$: Fisher's exact test; $^{\&}$:Chi-square test

5.3.2 Characteristics of vestibular symptoms

The attack frequency of vertigo varies significantly between three groups, as demonstrated in Table 12, the BtM group had the most frequent attacks, followed by the dMV and pMV groups, subsequently ($p<0.01$, Kruskal-Wallis test, degree of freedom=2). On the contrary, duration of vertigo did not show this relationship between three groups ($p=0.20$, Kruskal-Wallis test, degree of freedom=2). As for the migrainous symptoms, 13 subjects (87%) of the BtM group had experienced phonophobia during vertigo attacks, which was similar to that of dMV group (90%) but significantly higher than that of the pMV group (19%, $p<0.001$, Chi-Square test). Likewise, the occurrence rate of photophobia and scintillating scotoma was significantly higher in BtM and dMV patients than in pMV patients ($p<0.01$, Chi-Square test). Considering the presentation of motion sickness, occurrence rate was more common in BtM (80%) and dMV patients (83%) than pMV patients (53%, $p=0.02$, Chi-Square test).

Table 12. Characteristics of vestibular symptom among three diagnostic groups

Factors	Number of patients			p value
	BtM (n=15)	dMV (n=30)	pMV (n=32)	
Frequency				**<0.01#**
<5 times	0	3	13	
yearly	0	2	4	
monthly	4	14	6	
weekly	8	7	5	
>1/wk	3	4	4	
Migrainous symptoms				
Phonophobia	13 (87%)	27 (90%)	6 (19%)	**<0.001***
Photophobia	10	19	4	**<0.001***
Scintillating scotoma	5	10	1	**<0.01***
Motion sickness	12 (80%)	25 (83%)	17 (53%)	**0.02***

#: Kruskal-Wallis test, degree of freedom=2

*: Chi-square test, degree of freedom=2

5.3.3 Characteristics of migrainous headache

Attack frequency of headache showed non-significant difference across three groups ($p=0.24$, Kruskal-Wallis test). Regarding the sequential relationship between headache and vertigo, comparison of the three diagnostic groups had demonstrated a significant difference (Table 13, $p<0.001$, Fisher's exact test). Restated, subjects with BtM and dMV were more likely to exhibit a sequential relationship between headache and vertigo attacks (Table 13, 80% and 67% occurrence respectively), while most of the pMV patients experienced headache or vertigo independently (16% of concurrence). Details of the attack sequence between headache and vertigo were illustrated in Table13, i.e. headache precedes vertigo, vertigo precedes headache, and simultaneous headache and vertigo attacks, demonstrating non-significant difference between three diagnostic groups ($p=0.81$, Fisher's Exact test).

As regards to the migraine precipitants, occurrence rate among the three groups did not differ significantly ($p>0.05$, Chi-Square test, Table 14). Additionally, among female subjects with active menstruation cycle (N=70), the precipitation of migrainous headache during the menstruation period had an equal distribution across three groups ($p=0.99$, Chi-Square test).

Table 13. Sequential relationship between headache and vertigo attack among three diagnostic groups

Factors	Number of patients			p value*
	BtM (n=15)	dMV (n=30)	pMV (n=32)	
Unrelated	**3 (20%)**	**10 (33%)**	**27 (84%)**	**<0.001**
Related	**12 (80%)**	**20 (67%)**	**5 (16%)**	
Headache precedes	4	4	1	
Vertigo precedes	5	8	3	
Simultaneous	3	8	1	

*: Fisher's Exact test

Table 14. Distribution of migraine precipitants among three diagnostic groups

Migraine precipitants	Number of presence			p value*
	BtM (n=15)	dMV (n=30)	pMV (n=32)	
Sleep irregularity	11	24	23	0.74
Stress	12	22	18	0.18
Food	8	16	15	0.85
Menstruation[#]	6	13	13	0.99

*: Chi-Square test, degree of freedom=2

[#]: Female subjects with active menstruation cycle (n=70)

Comparing the neurological symptoms during migraine attack among the three groups, it revealed that the occurrence rates of bilateral paresthesia, dysarthria and ataxia in the BtM group were 67 %, 47 % and 47 %, respectively, showing significantly higher rates than those in the dMV and pMV groups (Table 15, $p<0.01$, Fisher's exact test). However, visual symptoms and drowsiness did not differ significantly among the three groups. Restated, the BtM group tends to experience transient neurological symptoms more often than the other two groups, in terms of paresthesia, dysarthria, and ataxia.

Table 15. Neurologic symptoms during migraine attack among three diagnostic groups

Migraine precipitants	Number of presence			p value
	BtM (n=15)	dMV (n=30)	pMV (n=32)	
Paresthesia	10 (67%)	3	3	**<0.01***
Dysarthria	7 (47%)	2	3	**<0.01***
Ataxia	7 (47%)	3	3	**<0.01***
Visual symptoms	7	7	5	0.07#
Drowsiness	8	11	11	0.44#

*: Fisher's Exact test

#: Chi-Square test, degree of freedom=2

5.3.4 Audiovestibular function tests

In audiometry, most subjects had normal hearing (p=0.40, Chi-Square test, Table 16). Similarly, result of caloric tests did not differ among three groups. Regarding the ENG examinations, patients with BtM had much higher rates of abnormalities on the saccade test than dMV and pMV patients (p=0.04, Chi-Square test). However, presence of spontaneous nystagmus and abnormalities on pursuit and OKN tests did not reach significant differences between three groups.

Table 16. Audiovestibular function tests among three diagnostic groups

Factors	Number of abnormalities			p value[#]
	BtM (n=15)	dMV (n=30)	pMV (n=32)	
Audiometry	1	0	1	0.40
Caloric test	4	5	7	0.72
Spontaneous nystagmus	4	8	8	0.99
OKN test	9	12	10	0.17
Saccade test	6	3	5	**0.04**
Pursuit test	5	7	6	0.55

[#]: Chi-Square test, degree of freedom=2

5.3.5 Multivariate analysis of differentiating factors

It is worth noted that some of the above-mentioned factors with significantly different distributions between three groups are partly included in the diagnostic criteria, i.e. migrainous symptoms (included in dMV), sequential relationship (BtM) and aura symptoms (BtM). Therefore, subsequent polytomous logistic regression was conducted with exclusion of these 3 factors, in order to prevent selection effect from diagnostic criteria. Comparison was analyzed using dMV as the baseline group. Other factors with significant difference between three groups were included, that is, motion sickness, frequency of attack, and saccade test. The results demonstrated that the presence of motion sickness was significantly different between dMV and pMV ($p<0.01$, polytomous logistic regression), while BtM and dMV had similar occurrence ($p=1$). In addition, the difference between BtM and dMV was significant when comparing the frequency of vertigo ($p=0.01$) and the abnormalities of saccade test ($p<0.01$), while no difference exist between dMV and pMV ($p=0.32$ and 0.47 for frequency of vertigo and abnormal saccade test, respectively). In other words, excluding those factors in relation to diagnostic criteria, multivariate analysis had also demonstrated a significant trend that BtM and dMV are similar clinically (motion sickness), while BtM had the most frequent attack and abnormal saccade test.

5.3.6 Treatment effectiveness of three diagnostic groups

Except 5 patients from the pMV group were lost from the clinic, 72 patients had completed the treatment course. Seven out of 15 subjects (47%) in the BtM group revealed good response of treatment, compare to 80% (24 / 30) and 70% (19/27) of the respective dMV and pMV groups (p=0.07, Chi-Square test, degree of freedom=2). Since the treatment effectiveness revealed non-significant difference between dMV and pMV groups, the outcome of BtM were compared with both groups of MV. Significant difference was noted that BtM had worse outcome compared to the combination of the two MV groups (Table 17).

Table 17. Treatment effectiveness among three diagnostic groups

Outcome	**Number of patients**		**p value**[#]
	BtM (n=15)	**Definite and probable MV (n=57)**	
Good response	7 (47%)	43 (75%)	0.03
Poor response	8	14	

[#]: Chi-Square test with correction of continuity

6. Discussion

6.1 Study population

In this prospective cohort study, 110 patients with migrainous headache and vertigo/dizziness were enrolled in a period of 7 months. All cases were treated with formulated medications and regularly followed at our clinic. Most of the demographic characteristics among the study population were compatible with the literature, including a mean age of 40 years old, female predominance (85%), strong family preponderance (72%), plateau of onset of symptoms around 20-29 years old, and headache as the first presenting symptom in 61% of subjects. (Kayan and Hood, 1984; Sturzenergger and Meienberg, 1985; Olsson, 1991; Cutrer and Baloh, 1992; Dieterich and Brandt, 1999). This excellent comparability with other series supports our study design and the algorithm of subject enrollment as described in section 4.1. In other words, the strict policy on excluding other potential diagnoses and following the IHS criteria leads to fruitful result in this study.

However, considering the early onset of symptoms, most of these middle-aged subjects are anticipated to suffer from prolonged duration of history. In fact, the median duration of history in the study population was as long as 17 years, which indicates that migraine-related vertigo and dizziness were not well understood in Taiwan, hence delayed diagnosis and inappropriate management were concerned.

6.2 Clinical manifestation of enrolled subjects

Previous reports had already pointed out a higher susceptibility of vestibular symptoms in migraineurs, e.g. vertigo, dizziness and motion sickness (Kuritzky et al., 1981; Kayan and Hood, 1984). In addition, migraine and associating migrainous symptoms were suggested as cardinal features of definite migrainous vertigo (Neuhauser, et al. 2001). Likely, our result also showed a higher rate (69%) of motion sickness among study population (Table 3), and about half of the subjects (49%) had noticed sequential relationship between headache and vestibular symptoms, corresponding with the literature. Further investigating the migrainous symptoms during vestibular episodes (Table 3), current study showed that phonophobia was noted in 58% of subjects, followed by photophobia (41%) and scintillating scotoma (27%). Opposite to photophobia as the most common symptom (Neuhauser, et al. 2001), this discrepancy may because the sampling of patient from a neurotological clinic, where the majority of complaints consisted hearing, vertigo and dizziness.

As mentioned before, a smaller proportion of migraine with aura (15%) was noted in our patients, consistent with a recent population based survey conducted in Taiwan that 12.5% of subjects had migraine with aura (Wang, et al., 2000). However, the presentation of aura in our series was quite different from the classical auras, i.e. visual, sensory and verbal. The most frequent auras in this study were vertigo (81%),

tinnitus and bilateral paresthesia (69%), indicating lesions affected the brainstem and/or the territory of posterior circulation. On the contrary, classical auras pointed to lesions in the cerebral cortex and/or the territory of anterior circulation. This discrepancy may also due to recruitment of patients from a vertigo clinic, filtering out most subjects with classical aura.

The result of audiovestibular function tests demonstrated normal audiometry in most subjects, while 41%, 22% and 17% of abnormalities were noted over OKN, pursuit and saccade tests, respectively (Table 5), compatible with a previous study by Liao and Young (2004). Although most subjects noted phonophobia during vestibular episodes (Table 3), which could be attributed to some extent of inner ear disturbance, only 2 subjects presented with abnormal hearing. In other words, conventional physiological tests such as audiometry may not be detective enough for minor dysfunction. Therefore, more sensitive modalities, such as otoacoustic emission (OAE) and other electrophysiological tests may help to reveal these subtle abnormalities in the future.

Interestingly, number of subjects presented photophobia during vestibular episodes equaled with subjects with abnormal OKN tests (n=45, Table 3 and Table 5). However, further examine the correlation between these two factors revealed non-significant result (Chi-Square test, p=0.87), despite the similar involvement of

visual stimulation for both photophobia and OKN tests. Otherwise, considering caloric test, the abnormal rate in the current study was much lower (21%) compared with Liao and Young's series (55%). This could be explained by the inclusion of directional preponderance as abnormal finding in the previous study, resulting in a higher rate of abnormalities. Similarly, higher abnormal rates can be noticed in other studies (Kayan and Hood, 1984; Dieterich and Brandt, 1999), which also include both canal paresis and directional preponderance. However, directional preponderance is non-specific for the lesion site and was no longer reported in our laboratory and hence, a lower abnormal rate in caloric test ensued.

6.3 Treatment effectiveness and its correlation with clinical manifestations

The treatment effectiveness in this series is satisfactory, with complete resolution and substantial control in 71% of subjects, similar to a 69% response rate reported in a previous series (Maione, 2006). Although the literature had already suggested that migraine prophylactic medications were also beneficial to migraine-related vertigo or dizziness (Slater, 1979), correlation between clinical characteristics and the treatment effectiveness remained unexplored. Therefore, it was our great interest to identify potential outcome predictors by ways of univariate and subsequent multivariate analysis.

The result demonstrated that age at presentation was one of the most important factor associated with treatment effectiveness, that is, younger patient correlated with poor response of medication ($p=0.05$, cumulative logits regression, $\beta=0.027$), and this association further augmented in multivariate analysis (Table 10, $p<0.01$, aOR=2.38 for each 10-year decline, 95% CI: 1.39 ~ 4.07). Conversely, age at onset of symptoms did not correlate with the treatment effectiveness, despite it may reflect the disease process more accurately if precisely measured. In the current study, loss of remote memory during interview could reduce the reliability of this information and hence, the actual level of association may be underestimated.

Frequent attacks of vertigo played another significant role in predicting the treatment effectiveness. The result showed that repeated attacks were associated with worse response, compared with sporadic ones (Table 10, $p<0.01$, aOR=7.73, 95% CI: 2.05 ~ 19.1). In other words, for subjects with more frequent vestibular symptoms, unsatisfactory response to medication can be anticipated. On the contrary, other vestibular characteristics, e.g. duration of vertigo and migrainous symptoms do not correlate with treatment effectiveness as well. Furthermore, the treatment effectiveness is similar regardless of whether a sequential relationship between headache and vestibular symptom is present (Bikhazi, e al., 1997). In summary, these factors can only be regarded as diagnostic reference without relevance to treatment effectiveness.

In this study, up to 96% of subjects reported at least one of the common migraine precipitants, including sleep irregularities, stress, food, and menstruation periods (Table 4). Among them, food was the only factor correlating with treatment effectiveness (Table 8 and Table 10). The reason why this information is worth discussion, despite its borderline statistical significance (Table 10, p=0.06, aOR=0.31, 95% CI= 0.09 ~ 1.04), is that it represents an "avoidable" factor among the migraine precipitants, since the exposure to other precipitating factors are less controlled. In other words, subjects with their symptoms provoked by exposure to specific food actually showed better outcome after avoiding them. Therefore, patient education becomes very useful and constitutes an important role for managing migraine- related vertigo and dizziness, especially for those with frequent contact with migraine-provoking food.

Of the female subjects with active menstrual cycle, 42 out of 85 patients complained a relationship between migraine attack and menstruation period, with 33 patients recognized headache before the menstruation period (Table 4). These subjects may represent a subgroup of "menstrually-related migraine", which had been suggested by the International Headache Society (IHS). A recent review by Recober and Geweke (2005) proposed estrogen withdrawal as the trigger of menstrual migraine attacks. Although our result did not show significant association between

treatment effectiveness and menstruation precipitance (Table 8, p=1), for those with poor control especially during the menstruation periods, additional NSAIDs or oral contraceptive can be given as an adjuvant therapy (MacGregor, 2000).

Except for the subjective symptomatology, neurotological assessment played another role for the correlation with treatment effectiveness. Although mixed central and peripheral abnormalities of audiovestibular function tests are frequently reported in cases of migraine-related vertigo and dizziness (Kayan and Hood, 1984; Cass, et al., 1997; Johnson, 1998; Dieterich and Brandt, 1999), by way of univariate and multivariate analyses, only OKN test was significantly correlated with outcome in the current study (Table10, $p<0.01$, aOR=5.40, 95% CI: 1.60 ~ 18.2). In other words, comparing with the non-significant correlation between treatment effectiveness and caloric test, central lesions as suggested by OKN abnormalities are strongly associated with less favorable response to treatment.

6.4 Relationship between different diagnostic groups

As mentioned in the literature review, various nomenclature and corresponding criteria had been proposed during the past decades. Basically, it is because that the IHS criteria of BtM can be fit in less than 10% of patients suffering migraine-related vertigo or dizziness (Dieterich and Brandt, 1999; Neuhauser, et al., 2001), resulting in a variety of diagnostic criteria and lack of global consensus (Appendix I). Hence, it is essential to conduct this comparative study, using the most widely accepted criteria, namely, basilar type migraine (BtM), definite migrainous vertigo (dMV) and probable migrainous vertigo (pMV), to examine whether these criteria referred to different diseases, or similar disease with different presentations.

Considering the characteristics of vestibular symptoms, BtM group had the most frequent vertigo attacks, followed by dMV and pMV (Table 12). Although wide distribution of attack frequency had been reported before (Dieterich and Brandt, 1999), such association between diagnostic groups has not been addressed. Besides, comparing migrainous symptoms during vertigo episodes, both BtM and dMV showed significantly higher occurrence rate than pMV in each of the symptoms (Table 12). Arguably, this result may due to selection effect of the diagnostic criteria for dMV. Serendipitously, occurrence rates of phonophobia, photophobia and visual symptoms are quite similar in the BtM group, despite the fact that migrainous

symptoms during vertigo episodes was not included in the diagnosis criteria of BtM. In addition, motion sickness is another dominant symptom in both BtM and dMV groups, with higher occurrence rates than pMV group (Table 12, p=0.02).

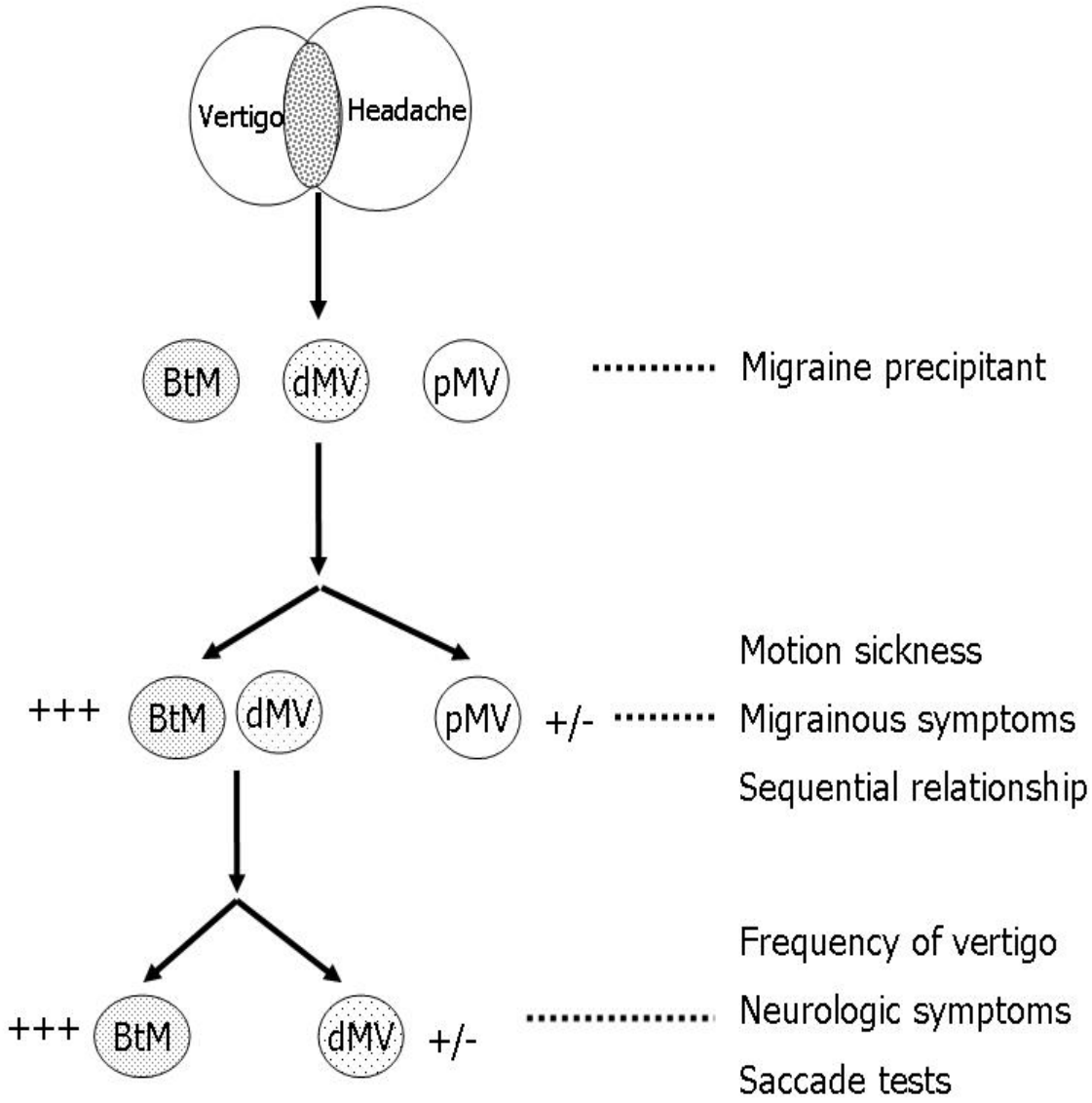
As for the characteristics of migrainous headache, it is well known that vestibular symptom may occur before, during, or even after migraine attack (Harker and Rassekh, 1987). In this study, BtM and dMV patients tend to have their vertiginous episodes related to migraine attacks more commonly, with the concurrence rates of 80% and 67%, respectively, compared to 84% of unrelated attacks in the pMV patients, exhibiting a significant difference (Table 13). Again, this finding could be related to selection effect from diagnostic criteria, since vertigo may present as an aura in BtM group, and migrainous headache during vertigo is also part of the criteria for dMV. As for the other characteristics, although the presence of migraine precipitants distributed similarly among groups (Table 14), neurologic symptoms are more frequently presented in the BtM group than the other two groups, especially in relation to bilateral paresthesia, dysarthria and ataxia (Table 15).

In this study, higher abnormal rates of saccade test were noted in the BtM group than the other two groups. The saccadic eye movement system passes from the frontal cortex, through medial longitudinal fasciculus (MLF), peri-pontine reticular formation (PPRF) to brainstem nuclei, in order to fix the moving object on the central fovea.

Therefore, abnormal saccadic tests in BtM cases served as the objective evidence of corresponding brainstem dysfunction, as suggested by the presence of neurologic symptoms. Furthermore, a previous study using vestibular evoked myogenic potential to evaluate subjects with basilar artery migraine also reflected a brainstem deficit (Liao and Young, 2004).

Accordingly, differentiation of BtM, dMV and pMV can be illustrated in Figure 3. First, when simply comparing the presence of migraine precipitants, the three groups have a similar presentation. Second, when looking at the clinical features, such as motion sickness, migrainous symptoms and sequential relationship between headache and vertigo, this study shows that BtM and dMV can be quite alike, while pMV is different from them, because of its less pronounced clinical features. Third, further investigating the attack frequency of vertigo, presence of neurologic symptoms and abnormal saccade tests, BtM can be differentiate from dMV by its higher frequency of attack, higher present rate of neurologic symptoms, and more abnormalities of saccade test.

Figure 3. Differentiation of diagnostic groups



One may suspect that this result of differentiation is due to selection effect from diagnostic criteria, since the presence of migrainous symptoms was included in the criteria of dMV, while sequential relationship and aura symptoms were included in the criteria of BtM. However, based on the multivariate analysis using only factors “not considered” in the diagnosis, i.e. motion sickness, frequency of vertigo, and saccade test, the result also demonstrated significant difference between dMV and pMV in terms of motion sickness. In addition, attack frequency of vertigo and abnormal rates of saccade test differed significantly between BtM and dMV as well. This result illustrated the trend of distribution in clinical manifestation and the corresponding differentiating algorithm was not simply a result of selection from diagnostic criteria, but actually reflects a spectrum of clinical manifestations across three groups. Additionally, the BtM group showed significantly poor effectiveness of treatment than the other two groups (Table 17), further supporting the trend of clinical severity among these three groups.

In summary, BtM patients had more frequent attacks of vestibular symptoms with prominent migrainous features, more likely to have concurrent vertigo and headache attacks, more extensive neurological symptoms, more central signs on ENG, and unsatisfactory treatment effectiveness. Regarding the dMV group, it had similar clinical presentations as BtM group, but differed by fewer neurological symptoms and

ENG abnormalities. For the pMV group, it represented those with the least severe clinical presentation. Both dMV and pMV groups had better treatment response. Therefore, the relationship between these three groups refers to a spectrum of severity among the clinical syndrome of migraine-related vertigo and dizziness.

6.5 Limitations

First of all, to differentiate migraine-related vertigo and dizziness from other vestibular disorders is of utmost importance. It is well known that migraine-related vertigo has a strong association with other clinical diagnoses, e.g. Meniere's disease, BPPV, and psychological dizziness (Lempert and Neuhauser, 2005). In addition, no available biological marker was related to this disease entity up to date. Therefore, all patients with headache and/or vertigo underwent a battery of audiovestibular function testing without exception. Additionally, excluding subjects with other disorders would lose some "overlapping" cases inevitably. As a result, only 20% of migrainous headache was recruited in this study (140 out of 700, Figure 1), compared to 38% of migraine in previous series of dizziness clinic (Neuhauser, et al., 2001) Therefore, the actual percentage of migraine and its associated vestibular symptoms is beyond our estimation.

Second, since all the information was based on face-to-face interview, recall bias may exist. For example, usually the exact age at onset of symptoms can not be accurately obtained, and hence a 10-year span is used in stead. Attack frequency and motion sickness can also be under-estimated since remote memory is loss. Further, none of our patients had recorded a headache diary, thus the precise duration and associated characteristics are hard to figure out. Therefore, we included subjects with

somewhat less distinct clinical presentations, as demonstrated in the subtype of "probable migraine", because excluding these subjects would result in losing 20% (23 out of 110) of eligible subjects and decreasing the statistical power even more.

Third, the study design has other flaws that may limit the interpretation of results. One is that since only the effectiveness of treatment was measured within the 3-month course of medication, long-term effectiveness, recurrence of symptoms, and the trend of propagation of clinical manifestation can not be judged by our results. Another drawback would result from using the follow-up rate at our clinic as a proxy of measuring compliance, since the more reliable "pill counting" method was not applied. As a result, the interpretation of treatment effectiveness should be carried with caution, since placebo effect may exist for those with poor drug compliance but still attend follow-up visits regularly.

7. Conclusion

In this study, we have successfully enrolled a representative sample of migraine-related vertigo or dizziness in Taiwan. The significant factors in relation to treatment effectiveness are identified, i.e. frequency of vestibular episodes, age at presentation, and OKN abnormalities, which may be beneficial to the future clinical practice. In addition, the relationship between different diagnostic groups is referred to a spectrum of clinical severity, with BtM presenting the most extensive involvement of the brainstem and the worst treatment effectiveness.

8. Perspectives

Future studies will continue in several ways. First, based on this collection of subjects, a case-control study is beneficial to investigate the progress of this disease entity, to assess the long-term outcome, and to observe the development of co-morbidities with close association with migraine, e.g. cerebral vascular events. Second, placebo-controlled or head-to-head studies can be conducted to test the treatment effectiveness for migraine-related vertigo and dizziness, by means of recording diary about migraine and vertigo and comparing the pre- and post-treatment attack frequencies. Third, applying newly-developed electrophysiological tests in migraine-related vertigo and dizziness may help to establish a clue of diagnosis and also the differentiation between different diagnostic groups.

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Appendix I. Summary of diagnostic criteria

	Migraine	Vertigo	Family History	Temporal sequence	Migrainous symptoms	Objective signs	Motion sickness	Migraine precipitant	Medication	Exclusion
Migraine-related vestibulopathy	●	●	●				●			●
Vestibular migraine	○	●							●	●
Migrainous vertigo (definite)	●	●		●	●					●
(probable)	●	●		○	○			○	○	●
Basilar type migraine	●	●		●	●					●
Migraine associated vertigo	●	●				●				●

● : Absolute requirement

○ : Partial requirement

Appendix II: Protocol of structured interview

Serial No: _____ Name: _____ Chart number: _____ Gender: M / F

Birth: ___/____/____紀錄: ___/____/____ Education: _____ Tel:_____

Vertigo/Dizziness, Duration:(sec, min, hour) Freq: (<3 times, <1/Y , <1/M , <1/wk , ≥1 /wk)

時序(無, 同時, M->V, V->M), photophobia (+, −), phonophobia (+, −), scintillation (+, −)

Ver(<10, 10~, 20~,30~,40~), Mig(<10, 10~, 20~,30~,40~), 發病順序 (同時, M->V, V->M)

Headache Duration: (<2 / 2-4 / 4-72 / >72 hrs) Freq: (<5 times, <1/Y, <1/M , <1/wk, ≥1/wk)____

unilateral (+, −), pulsating (+, −), Mild / Mod / Severe, phys. act. (+, −), _____

N/V (+, −), photophobia (+, −), phonophobia (+, −), scintillation (+, −), _____

Classification: Migraine / Tension / Cluster / Others _____

Aura dysarthria (+, −), vertigo(+, −), tinnitus (+, −), hypacusia(+, −), aural fullness(+, −)

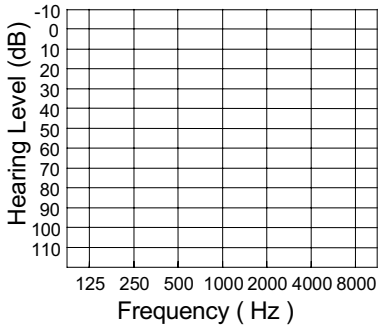
diplopia (+, −), visual symptoms(+, −), ataxia (+, −), decreased cons. (+, −) paresthesia (+, −)

Duration: <5min / 5-60 min / >60 min, temporal relationship (+, −)_____

MC (+, −) pre / during / post **Response to Mx** (+, −)初( ) **Sleep irregularities**(+, −)

Motion sickness (+, −)_____ **Smoking** (+, −)_____ **Stress**(+, −)

Family History (+, −) **Audiometry**



ENG No. _____ EO_____ EOD_____ EC_____ MA_____

Pursuit (N, abn); Saccade (N, abn); OKN (N, abn); **Caloric** (20 / 0 °C) abn EM:_____

R ___min _____s freq____/10s reg / hyper/petit/dys_____ VS_____VEMP_____

L ___min _____s freq____/10s reg / hyper/petit/dys_____ VS_____VEMP_____

Diagnosis: ___Migrainous vertigo ___Basilar type migraine ___ Migraine without aura

___Others_____ ___to be excluded

Appendix III: Informed Consent

台大醫院耳鼻喉部

眩暈及偏頭痛研究計畫病患同意書

各位病友您好:

偏頭痛及眩暈都是十分常見且困擾的疾病，根據估計台灣地區約有 60 萬名患者之多! 但對於此一病症至今仍然缺乏完整的認識。因此，本團隊特進行本研究計畫，以期日後能嘉惠更多同受此病所苦的患者。在此，感謝你撥冗配合本研究，本研究的內容包括:

1. 5-10 分中的詳細問診及訪談，

2. 1 份飲食情況調查表，填寫時間約 3 分鐘，

3. 日後如有需要時，會查詢您的就醫紀錄(檢查結果、用藥紀錄…等等)以及相關的健保資料以供追蹤分析。

再次感謝您的配合!

王棨德 醫師

楊怡和 教授

敬　　上

同意人: _____

Appendix IV: Food precipitation inquiry

No _____ 姓名 _____ 病歷號碼 _____ 填寫時間 _____/_____/_____

請您根據最接近實際的狀況來圈選以下的問題。

請注意: 以下所問的問題是指在你**開始治療偏頭痛及頭暈之前(也就是開始有醫師提醒您有些食物不能吃之前!)**

種類	不吃	每週少於 1 次	每週 1 次	每週 2-3 次	每週 4-6 次	每天 1 次	每天超過 2 次	是否曾經因吃了這種食物後發生頭暈或頭痛?
1. 牛奶	**0**	**1**	**2**	**3**	**4**	**5**	**6**	是 否
2. 優格/優酪乳/養樂多	**0**	**1**	**2**	**3**	**4**	**5**	**6**	是 否
3. 起司	**0**	**1**	**2**	**3**	**4**	**5**	**6**	是 否
4. 奶茶/加牛奶的咖啡	**0**	**1**	**2**	**3**	**4**	**5**	**6**	是 否
5. 柳橙/橘子 (產季時)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	是 否
6. 蕃茄(產季時)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	是 否
7. 葡萄柚(產季時)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	是 否
8. 巧克力	**0**	**1**	**2**	**3**	**4**	**5**	**6**	是 否
9. 紅酒	**0**	**1**	**2**	**3**	**4**	**5**	**6**	是 否
10. 冰品	**0**	**1**	**2**	**3**	**4**	**5**	**6**	是 否