J Neurol (1999) 246 : 883–892

ORIGINAL COMMUNICATION

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Episodic vertigo related to migraine (90 cases): vestibular migraine?

Received: 22 September 1998
Received in revised form: 3 March 1999
Accepted: 16 March 1999

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Abstract A retrospective study was conducted on 90 patients with episodic vertigo that could be related to migraine as the most probable pathomechanism. Since the majority of the patients did not fulfill the criteria of the International Headache Society (IHS) for basilar migraine, the diagnosis was substantiated by disease course, medical efficacy in treating (ergotamines) and preventing (metoprolol, flunarizine) attacks, ocular motor abnormalities in the symptom-free interval, and careful exclusion of the most relevant differential diagnoses, such as transient ischemic attacks, Menière's disease, and vestibular paroxysmia. The following clinical features were elaborated. The initial manifestation could occur at any time throughout life, with a peak in the fourth decade in men and a "plateau" between the third and fifth decades in women. The duration of rotational (78%) and/or to-and-fro vertigo (38%) could last from a few seconds to several hours or, less frequently, even days; duration of a few minutes or of several hours was most frequent. Monosymptomatic audiovestibular attacks (78%) occurred as vertigo associated with auditory symptoms in only 16%. Vertigo was not associated with headache in 32% of the patients. In the symptom-free interval 66% of the patients showed mild central ocular motor signs such as vertical (48%) and/or horizontal (22%) saccadic pursuit, gaze-evoked nystagmus (27%), moderate positional nystagmus (11%), and spontaneous nystagmus (11%). Combinations with other forms of migraine were found in 52%. Thus, migraine is a relevant differential diagnosis for episodic vertigo. According to the criteria of the IHS, only 7.8% of these patients would be diagnosed as having basilar migraine. However, to ensure that at least those presenting with monosymptomatic episodic vertigo (78% in our study) receive effective treatment, we propose the use of the more appropriate term "vestibular migraine."

Key words Vestibular migraine · Episodic vertigo · Ocular motor disorders · Migraine treatment

Introduction

The International Headache Society (IHS) requires an aura with two or more aura symptoms originating from the brainstem, usually developing over 5–20 min, and lasting no longer than 60 min to qualify as criteria for basilar migraine [37]. Thus, by definition, purely monosymptomatic attacks with rotational vertigo for seconds to a few minutes cannot be called basilar migraine or "migraine with acute onset aura," which requires further neurological symptoms that develop within 4 min. The latter diagnosis is considered even less appropriate if the attacks are not followed by headache. However, experts of dizziness units increas-

ingly report the common experience that episodic vertigo of shorter (seconds to minutes) or longer duration (several hours to days) – than that defined by the current classification – may indicate migraine attacks even if they occur without associated headache (R.W. Baloh, A. Bronstein, T. Lempert, L. Luxon, personal communications).

We diagnosed migraine as the most probable cause of episodic vertigo in the 90 patients reported on here by three means: (a) careful clinical exclusion of relevant differential diagnoses such as transient ischemic attacks, Menière's disease, and vestibular paroxysmia (neurovascular cross-compression of the eighth nerve); (b) the patient's positive response to migraine medication during the attack (ergotamines) and/or to prophylactic medication (metoprolol, flunarizine); and (c) follow-up of these patients over 2–7 years. The study design must be retrospective, as we learned from our own difficulties in defining the disease and the frustrating attempts to treat these patients with antiplatelet agents, anticoagulation, betahistine, or carbamazepine when one of the above major differential diagnoses was suspected. The positive response of these patients to migraine medication encouraged us to present this clinical report on the variable spectrum of episodic vertigo in migraine, despite the classification problem, of which we are fully aware. In contrast to earlier studies, the efficacy of antimigraine treatment was used as an additional determinant to establish the diagnosis in these 90 patients. This probably aided us in identifying unusual monosymptomatic forms of migraine which otherwise might have gone undetected or been mislabeled. To improve the diagnostic criteria of migraine manifesting primarily in the vestibular system, the following aspects seemed to require further discussion: duration and frequency of the attacks, number of aura symptoms, vestibular and ocular motor signs during the attack and in the symptom-free interval, association of vertigo attacks with headache, association of episodic vertigo with other forms of migraine, age at onset, and efficacy of medical treatment.

Material and methods

From January 1989 to April 1996, 1500 outpatients were referred to the Dizziness Unit at the Department of Neurology, University of Munich. Ninety patients (6.0%) were selected, in whom the final diagnosis of episodic vertigo related to migraine had been made, and for whom complete clinical records were available (Table 1). The authors saw all patients (54 women, 36 men) who underwent appropriate examinations to rule out thromboembolic ischemic events by computed tomography, magnetic resonance imaging of the brain, and ultrasound Doppler sonography. In older patients with frequent episodes even trial treatment with antiplatelet drugs or anticoagulants was performed without success. They were included in the study only if medical migraine prophylaxis abolished the attacks. Some of the patients were examined with electroencephalography and had acoustic evoked brainstem potentials and audiograms determined if necessary. Neuro-otological and neuro-ophthalmological evaluation included electronystagmography in 87 patients (with bithermal caloric testing in 84 patients), and orthoptic analysis in 62 patients with testing of the otolith function by means of psychophysical adjustments of perceived vertical and measurements of ocular torsion (by fundus photographs). All patients were seen at least twice; some (59%) were followed over 2–7 years.

Table 1 Frequency of various vertigo syndromes in 1370 outpatients of a dizziness unit (1989–1995)

Vertigo syndrome	*n*	%
Benign paroxysmal positioning vertigo	258	18.8
Phobic postural vertigo	196	14.3
Central vestibular vertigo	185	13.5
Menière's disease	101	7.3
Vestibular migraine	83	6.0
Vestibular neuritis	67	4.9
Psychogenic vertigo (without phobic postural vertigo)	41	3.0
Bilateral vestibulopathy	31	2.3
Vestibular paroxysmia (disabling positional vertigo)	24	1.8
Perilymph fistula	3	0.2
Other rare causes (determined)	31	2.3
Vertigo of unknown etiology	64	4.7
Central vestibular syndromes without vertigo[a]	186	13.6
Diseases without vertigo[b]	100	7.3

[a] Brainstern syndromes with ocular motor and vestibulospinal deficits, for example, after strokes, without vertigo
[b] For example, ocular motor disturbances of other origin such as ocular myasthenia, peripheral nerve palsies, and symptoms incorrectly termed vertigo or dizziness such as dementia and unsteadiness in sensory polyneuropathy

Since most of the patients (n = 83) did not fulfill the IHS criteria for basilar migraine but could be cured by medical migraine treatment, diagnosis of episodic vertigo or dizziness related to migraine was based, first, on the history of at least five attacks in which vertigo or dizziness was a major complaint in any period of time, and second, on one of the following four typical groups (A–D) into which the response to migraine treatment was included:

Group A
- Recurrent attacks of vertigo or dizziness and *nonvestibular* neurological deficits attributable to a dysfunction in the brainstem
- Associated headache during or immediately after vertigo or dizziness ("brainstem aura with headache")
- Individual history of migraine

Group B
- Recurrent attacks of vestibular and/or ocular motor dysfunction only
- Associated headache during or immediately after vertigo or dizziness ("only vestibular or ocular motor aura with headache")
- Individual history of migraine

Group C
- Recurrent attacks of vestibular and/or ocular motor dysfunction only
- Associated headache during or immediatly after vertigo or dizziness ("only vestibular or ocular motor aura with headache")
- Efficacy of medical (migraine) treatment

Group D
- Recurrent attacks of vestibular and/or ocular motor dysfunction only
- *Without* associated headache during or immediately after vertigo or dizziness ("only vestibular or ocular motor aura without headache")
- Efficacy of medical (migraine) treatment

These categories allowed us to define constellations based on the minimal features necessary to assess the diagnosis. All our patients showed the features of at least one of these constellations. Many presented with features of more than one category, especially when observed over a longer time. Efficacy of medical treatment of migraine in categories C and D means that either acute attacks were suppressed by ergotamines (n = 14) and/or the frequency of the attacks was significantly reduced by preventive medication with beta-blockers (metoprolol; n = 16), calcium antagonists (flunarizine; n = 5) [14, 56] or both (n = 2). From the 90 patients with episodic vertigo or dizziness 17 (19%) we assigned to group A, 36 (40%) to group B, 20 (22%) to group C, and 17 (19%) to group D.

None of the patients showed typical signs and symptoms of Menière's disease or neurovascular compression of the eighth nerve at first examination or follow-up. In older patients it is often difficult to differentiate basilar migraine from transient ischemic attacks. Thus, we at first treated a presumed ischemia with antiplatelet agents or anticoagulation. If this therapy failed and recurrent monosymptomatic attacks occurred without other brainstem signs and symptoms, migraine was assumed, and treatment with beta-blockers was tried. Diagnosis in these older patients was then made on the basis of the efficacy of prophylactic migraine treatment over a period of at least 6 months.

Results

Attacks that met the IHS criteria of basilar migraine occurred in only 7.8% of the patients (n = 7). The reasons for not fulfilling the criteria were monosymptomatic auras in 77%, too short (12%) or too long (41%) duration of the episodes, or a prolonged episode of several aura symptoms in 16% (Table 2). Data on the 90 patients with episodic vertigo were analyzed with respect to the following relevant aspects: duration and frequency of the attacks, number of aura symptoms, vestibular and ocular motor signs during the attack and in the symptom-free interval, association of attacks with headache, association with other forms of migraine, age at onset, and efficacy of medical treatment.

Table 2 Classification of attacks according to the IHS criteria

Aura characteristics	*n*	%
Meet the IHS criteria for basilar migraine	7	7.8
Two or more symptoms, duration 5–60 min		
With headache	5	
Without headache	2	
Do not meet the IHS criteria for basilar migraine	83	92.2
Two or more symptoms, but duration > 60 min		15.6
With headache	9	
Without headache	5	
One symptom, duration 5–60 min		23.3
With headache	10	
Without headache	11	
One symptom, duration > 60 min	41.1	
With headache	29	
Without headache	8	
One symptom, duration < 5 min		12.2
With headache	8	
Without headache	3	

Aura symptoms

Episodic vertigo was classified as vestibular in 84 patients; the remaining six patients had light-headedness and non-vestibular ocular motor dysfunction causing oscillopsia or double vision (Table 3). The prevailing type of vertigo was rotational in 70 of the 84 patients. Fourteen of these patients with episodic rotational vertigo also reported positional vertigo or significant modulation of the intensity of vertigo in certain head positions. Episodic positional vertigo was the sole vestibular symptom in one patient. The second most common type was to-and-fro vertigo (n = 34). Both sensations were associated with postural imbalance and unsteadiness. Rotational and to-and-fro vertigo occurred in combination (n = 22) in single or subsequent attacks. Severe unsteadiness with only slight dizziness was reported by only one patient. An overview of the frequency and duration of the attacks is given in Table 3. Unspecific descriptions, such as light-headedness, were not taken into consideration for the statistical analysis since their connection with vestibular function was questionable.

It was striking that 56 patients (62%) could be classified – on the basis of their episodic vertigo – as a *monosymptomatic vestibular group*. Associated auditory symptoms occurred in an additional 14 patients (16%); these included tinnitus (n = 9), episodic hearing loss (n = 3), and pressure in the ear (n = 2). Thus 70 patients (78%) presented with only audiovestibular symptoms.

More complex (multisymptomatic) neurological deficits associated with vestibular dysfunction were found in a group of 13 patients (14%). These included dysarthrophonia (n = 7); numbness of hand, face, or leg (n = 7); double vision; paraparesis; visual field defects; hearing loss; and lack of concentration (n = 1 in each).

Table 3 Characteristics of vertigo attacks in 90 patients (more than one feature could be reported in single or subsequent attacks)

	Rotational vertigo	To-and-fro vertigo
Single attacks	70	34
Duration: seconds	7	2
Duration: < 5 min	15	3
Duration: 5–60 min	8	6
Duration: hours	27	14
Duration: 1–4 days	13	9
Multiple attacks	62	33
Times per day	1	4
Times per week	17	11
Times per month	26	11
Times per year	18	7
Positional vertigo	14	0
Positional vertigo only	1	
Light-headedness and gait ataxia only	1	
Light-headedness and ocular motor disturbances	6	

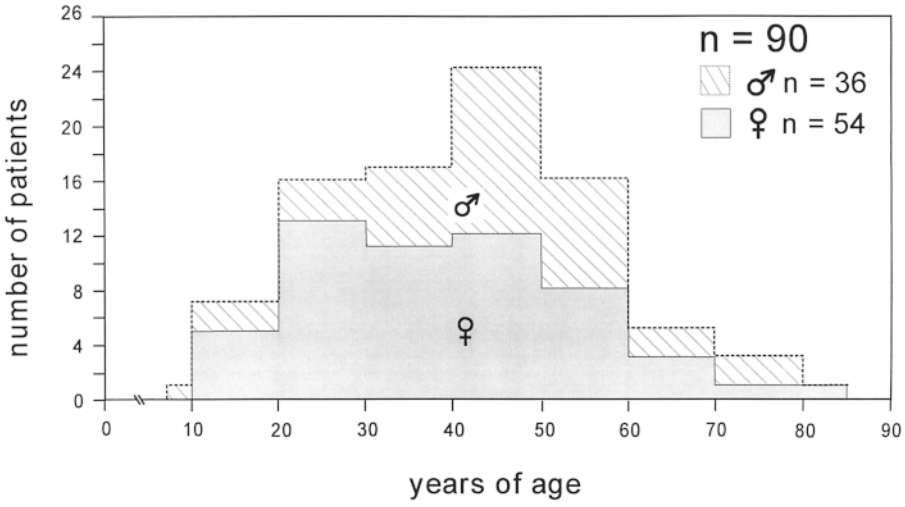

Fig. 1 Age at first manifestation in 90 patients with episodic vertigo related to migraine, appearing with recurrent vertigo and/or ocular motor disorders

The third group of 7 patients (7.8%) experienced only *nonvestibular dizziness (light-headedness) with neurological brainstem deficits* due to a combination of ocular motor palsy and involuntary ocular oscillations (n = 5); dysarthrophonia (n = 3); numbness of the face, hand, or leg (n = 3); disturbances of consciousness (n = 3); and visual field defects (n = 2).

The precise ocular motor dysfunction in the attack could be observed in only eight patients and remained unknown in the others. All statistics on signs and symptoms in basilar migraine or episodic vertigo related to migraine suffer from the fact that the patients are usually examined in the symptom-free interval or during recovery from an attack. Symptoms of the neurological brainstem deficits are based on anamnestic data.

Age at onset

The first vertigo attack occurred between the ages of 10 and 72 years in women and between 7 and 72 years in men; the female-male ratio was 1.5:1. The mean age among women was 37.7 years, with a plateau in the third to fifth decades (Fig. 1); the mean age among men was 42.4 years, with a peak in the fifth decade. The very first attack can manifest in both men and women as late as in the 60 s, without recall of a prior experience of migraine attacks. Mean duration of the condition before diagnosis of migraine was 3.7 years in women (range 3 weeks–30 years) and 5.7 years in men (range 4 weeks–37 years).

Association of episodic vertigo with headache

In 61 patients (68%) the attack was associated with moderate (rarely severe) bilateral pain in the neck and occiput (n = 22, 24%), a holocephalic headache with pressing or tightening quality (n = 25, 28%), or a feeling of fullness in the head (n = 4, 4.4%). A severe unilateral temporal or frontal headache was reported by only 11 patients (12%); 29 patients (32%) could not recall headache or, for example, a feeling of fullness in the head either during or associated with the vertigo attacks. Thus, milder and more diffuse localized forms of headache prevailed.

Association with other forms of migraine

The described attacks were the only manifestation of migraine in 43 patients (48%), while 47 patients (52%) reported other forms of migraine: 42 migraine without aura and 5 migraine with aura (with other neurological symptoms). Migraine without aura manifested only before the first vertigo attack in 11 patients (with a migraine-free interval in 8 patients lasting 2, 8, 10, 12, 15, 25, 30, and 40 years) and alternated with episodic vertigo over the same time span in 10 (21%). In those who reported alternating migraine attacks in overlapping time spans (n = 26, 55%) migraine without aura as a rule developed first (n = 24, 51%). The headache in migraine without aura was generally located unilaterally in the temporal (n = 25), frontal (n = 8), or occipital (n = 7) regions. Only three patients localized it bilaterally in the parietal regions and one in the neck. The frequency of migraine attacks without aura could be reliably determined in 37 of 47 patients. It varied between monthly (n = 20), weekly (n = 10), and yearly (n = 7) attacks.

Accompanying symptoms were nausea and vomiting in 27 patients, photophobia in 23, “swimming in front of the eyes” in 10, phonophobia in 7, and an incapacitating fatigue in 3.

The family history of migraine was determined in 71 patients. It was positive for the mother in 29 patients, father in 4, sister in 5, brother in 6, children in 3, and grandmother in one. Ten patients had no family history of migraine, and in another 13 it was questionable (tension-type headache without accompanying migraine symptoms).

From the 17 patients with episodic vertigo attacks *without* associated headache (category D) only 3 had no association with other forms of migraine and two of them no family history of migraine. The other 14 had migraine without aura which manifested only before the vertigo attacks ($n = 2$), in parallel ($n = 9$), or years after the beginning of the vertigo attacks ($n = 3$). Family history of migraine in these patients was positive in 5, negative in 4, and unknown in another 5.

Only two women (38 and 48 years of age) had a history of stroke, both within the internal capsule (2.2%).

Vestibular and ocular motor deficits in the symptom-free interval

A surprisingly high percentage of patients (59 of 90 patients, 65.6%; from all four categories A–D) exhibited central vestibular or nonvestibular ocular motor signs independent of the attacks and without subjective complaints or additional brainstem signs. Most frequent were vertical (48%) and horizontal (22%) saccadic pursuit, gaze-evoked nystagmus (27%), moderate positional nystagmus (11%), spontaneous nystagmus with eyes closed and when observed with Frenzel's glasses (11%), dissociated gaze-evoked nystagmus (9%), and downbeat/upbeat nystagmus (3.3%; Table 4). Pathological value of the signs was interpreted according to the patient's age. Deficits were moderate and showed some variation in subsequent evaluations between the attacks but did not completely disappear even under effective prophylactic migraine treatment. Only 23 patients (25.6%) had no abnormal ocular motor function in the symptom-free interval. Neuro-ophthalmological evaluation of eight patients was biased and limited due to congenital strabismus or congenital nystagmus.

Table 4 Central ocular motor signs in the symptom-free interval (*VOR* vestibulo-ocular reflex)

	n	%
Normal	23	25.6
Congenital strabismus	5	5.5
Congenital nystagmus	3	3.3
Central ocular motor signs[a]	59	65.6
Saccadic pursuit		
Vertical	43	48
Horizontal	20	22
Gaze-evoked nystagmus	24	27
Spontaneous nystagmus (> 50°/s)[b]	10	11
Positional nystagmus	10	11
Dissociated gaze evoked nystagmus	8	9
Downbeat nystagmus	3	3.3
Upbeat nystagmus	2	2.2
Impaired fixation suppression of VOR	3	3.3
Nuclear oculomotor palsy	1	1.1

[a] Multiple answers possible
[b] In combination with other central ocular motor signs and/or a directional preponderence in caloric testing

Electronystagmography and orthoptic analysis

Electronystagmography was performed in 87 patients (97%) at least once in the symptom-free interval. This included caloric testing with 44°C warm and 30°C cold water in 84 patients. Caloric testing during the symptom-free interval was normal in 66 patients, showed a peripheral vestibular hyporesponsiveness in 7 (1 acute deficit, 6 centrally compensated old deficits) without associated hearing loss, and a (central) directional preponderance in another 11 without peripheral vestibular lesion. Moderate central ocular motor signs were seen in 27 patients using electronystagmographic analysis (23 smooth pursuit deficits and gaze-evoked nystagmus, 17 directional preponderance in rotating tests, 11 impaired fixation supression of the vestibulo-ocular reflex, 3 saccadic dysmetria).

In the vertigo-free interval a complete orthoptic examination was performed in 62 patients (including examination of otolith function by psychophysical determination of subjective visual vertical and fundus photographs for determination of ocular torsion [16]). In 38 patients (61%) tests were normal, 8 had congenital abnormalities (5 strabismus, 3 congenital nystagmus), and 16 (26%) showed moderate central vestibular signs in the symptom-free interval (16 smooth pursuit deficits, 8 pathological deviations of subjective visual vertical, 5 positional nystagmus).

Eight patients were examined *during their vertigo attacks*: all had a transient spontaneous nystagmus (> 5°/s SPV), three patients had gaze-evoked nystagmus, three had a severe positional nystagmus (vertical direction, not habituating), two had a severe saccadic pursuit, and one a directional preponderance in the rotating and caloric tests.

Discussion

Episodic vertigo related to migraine: vestibular migraine?

This retrospective study of episodic vertigo and ocular motor disorders not only confirms the heterogeneous spectrum of neurological deficits attributable to a dysfunction in the brainstem but also provides us with further vestibular and ocular motor features hitherto not considered typical of migraine. Attacks with predominantly monosymptomatic vertigo without other severe neurological deficits can be attributed either to the labyrinth or to neurons of the pontomedullary region, including the vestibular nuclei. Attacks with more complex deficits including nuclear and supranuclear ocular motor signs seem to involve the brainstem more diffusely, affect consciousness more frequently, and thereby fulfill the diagnostic criteria of basilar mi-

graine. However, 92% of the patients described in this study did not fulfill the criteria for basilar migraine, mainly because they had monosymptomatic episodes, with duration either shorter or longer than the aura duration as defined by the IHS for basilar migraine. It seems more appropriate to group these patients under the descriptive term "vestibular migraine."

Strictly speaking, vestibular migraine also originates from the brainstem, independently of whether peripheral labyrinthine and/or central vestibular structures are affected. A comparable terminological problem exists for ophthalmoplegic migraine, which originates from a dysfunction in the ocular motor nucleus or fascicle in the mesencephalic brainstem (also supplied by the basilar artery territory).

Other authors have described earlier cases of episodic vertigo in migraine which support the heterogeneous spectrum of migrainous vestibular dysfunction [12, 39, 53]. Migraine with episodic vertigo in our study can manifest at any age, with a mean of about 40 years; it is not only a disorder of the adolescent girl, as claimed in the original description of basilar migraine by Bickerstaff [6]. The onset of vertigo at the age of 40 years or older was also found in two important clinical studies. The one by Kayan and Hood [39] particularly emphasized visual, ocular motor, and auditory abnormalities, and that by Sturzenegger and Meienberg [58] demonstrated that basilar migraine occurs throughout life (from 10 to 62 years) with varying symptoms and a surprisingly high incidence of impaired consciousness (77%). We found a plateau for first manifestation in the third to fifth decades in women (several postmenopausal) and a peak in the fifth decade in men. This contradicts the previous finding [58] that 65% of patients have their first attack in the second or third decade and then experience a gradual decline. There is only a slight sexual preference (women to males = 1.5:1). One-third of our patients (independently of age) did not complain of headache associated with aura deficits. The duration of vestibular and ocular motor dysfunction varied, ranging from seconds to hours or even days; the duration of a few minutes or several hours was most frequent. This is in accordance with the bimodal distribution for duration of minutes to 2 h and longer than 24 h as described by Cutrer and Baloh [12]. One could speculate that the shorter episodes are aura symptoms, whereas the long-lasting vertigo over days indicates motion intolerance and motion sickness associated with migraine. Other studies report that basilar migraine deficits typically last only a few seconds to minutes [39] or 30–60 min [6]. The variability of the duration of attacks bears a considerable impact on the differential diagnosis, which includes very short events for seconds, as in vestibular paroxysmia [8, 38]; longer-lasting attacks for hours, as in Menière's disease; and variable duration, as in transient ischemic attacks. Many of the ocular motor findings in our study during the attack and particularly in the symptom-free interval are incompatible with Menière's disease (see below). The combination of vestibular and auditory symptoms – typical of Menière's disease or vestibular paroxysmia – was comparatively rare (16%) in our study.

It was empirical experience with trial medications which taught us the importance of migraine symptoms for diagnosis. Differential diagnosis with transient ischemic vertebrobasilar attacks may be difficult or impossible for a single or a few attacks, since headache may or may not occur in both conditions. Recurrent, purely monosymptomatic audiovestibular or ocular motor attacks are atypical of transient ischemic brainstem attacks, which have other posterior circulation symptoms in addition [2, 22] and thereby support the diagnosis of migraine. Sometimes ongoing monosymptomatic attacks during the administration of prophylactic antiplatelet drugs finally led to the appropriate diagnosis.

Benign paroxysmal vertigo of childhood (BPVC) [5, 18, 21, 24, 25, 33, 42] and benign recurrent vertigo in adults (BRV) [44, 55] are commonly regarded as migraine equivalents [23, 25, 41, 44, 55]. Transitions are possible from the apparently distinct entity of BPVC to benign paroxysmal torticollis in infancy as well as to basilar migraine. To date there is little information on the origin and site of the vertigo in both conditions, and there is no convincing evidence that it should be located in the posterior temporal cortex as Eviatar proposed [23]. He interpreted the directional preponderance in caloric testing as indicative of a temporal lobe dysfunction. This view cannot be maintained, since distressing rotational and to-and-fro vertigo are extremely rare conditions in temporal lobe dysfunction [7]. As noted above, it is quite likely that the brainstem is involved, thus making both conditions variants of basilar migraine. As helpful as it may be to use a particular label for this condition in childhood and adulthood, both conditions come closest to the 78% of monosymptomatic vestibular cases in our study. Three children and several adults in our study – seen after the first attacks – could have been classified as having BPVC or BRV. Over longer observation periods, however, an increasing number of them developed additional signs and symptoms of basilar migraine. Consequently these patients would have been given two different subsequent diagnoses, although the underlying mechanism remained the same. Transition into and association with other forms of migraine are typical features of BPVC, BRV, and the "vestibular migraine" that we describe. Furthermore, "vestibular migraine," BPVC, and BRV respond to the same treatment.

Ocular motor deficits in the symptom-free interval indicate permanent brainstem or cerebellar dysfunction

The surprisingly high incidence (65%) of pathological ocular motor findings of *central* origin in the symptom-free interval agrees with the report by Kayan and Hood [39], who – in reference to the attack – described "findings in-

dicative of definite dysfunction of the vestibular and/or cochlear systems in 77.5% of their patients, half with central and half with peripheral pathology" (18.8% central, 28.8% peripheral, 30% inconclusive). Their study, however, provides no data on neuro-otological disturbances in the symptom-free interval. The high frequency (21%) of *persisting peripheral* vestibular deficits in the study by Cutrer and Baloh [12] was not confirmed in our study (8.3%). Objectively measurable electronystagmographic abnormalities (57–80%) were stressed earlier by Dürsteler [19], Toglia et al. [59], and Eviatar [23]. Kayan and Hood [39] speculatively interpreted these findings as follows: "most migrainous complications are caused by ischemia of sufficient severity to produce infarction of nervous tissue occurring during the vasoconstrictive phase of the attack." As attractive as this explanation appears, it is not supported by the complex pathomechanisms of migraine currently under discussion. During the aura phase an inhibition of cortical neuronal activity obviously causes the neurological symptoms and induces a reduction in regional cerebral blood flow, as shown by focal hypoperfusion in the posterior brain regions by the xenon-inhalation technique [47]. The pattern of reduced blood flow does not coincide with areas of cerebral blood supply, and transcranial Doppler studies do not show significant changes in blood flow velocities in the middle cerebral and basilar arteries during aura or headache phases of a migraine attack [13, 15, 28].

The heterogeneous results of previous studies of cerebral blood flow were due to varying techniques and methodological problems, for example, migraine attacks with and without aura were not differentiated. Overall, however, no significant regional blood flow changes have been reported during the headache phase of migraine without aura (single photon emission computed tomography [26]). Thus, arterial vasoconstriction alone cannot be the underlying mechanism. Instead, changes in neuronal activity in the dorsal raphe nucleus and the locus coeruleus of the brainstem – centers of autonomic control of cerebral and dural blood flow and antinociception [31] – were found to excite efferent neurons in the trigeminal nuclei and thereby cause vasodilatation of dural arteries, plasma extravasation, release of vasoactive substances (serotonin, calcitonin gene-related peptide, substance P), activation of prostaglandins, and degranulation of mast cells [1, 45]. The resulting perivascular aseptic inflammation of arteries in the dura mater, which are provided with afferent (C fibers) and efferent sensory fibers of the trigeminal nerve [20], induces the typical headache via the central trigeminal nucleus. The extension of the trigeminal nucleus down to the cervical cord (C2) and its projections to neurons that receive afferent fibers from upper cervical roots may explain the localization of pain in the neck and occiput [14, 32], the most frequent sites of pain in basilar migraine but not in migraine without aura. Coactivation of certain brainstem nuclei may result in accompanying symptoms such as polyuria, perspiration, arterial hypotension, nausea, and vomiting. The important role of the brainstem in the pathophysiology of migraine is supported by positron-emission tomography [61], which in patients with unilateral migraine without aura has exhibited a bilaterally increased blood flow in cingulate, auditory, and visual association cortices during the attack, and a *persisting* brainstem activation during the symptom-free interval. This significant, slightly lateralized activation in the symptom-free interval was detected over several planes of the brainstem from the pons to the midbrain in the periaqueductal gray matter and the midbrain reticular formation. Maximal activation seemed to occur in the dorsal raphe nucleus and the locus coeruleus [61].

All these findings point to a mechanism of neuronal dysfunction that is triggered by certain brainstem centers [43]. When we consider that migraine aura is a neurally driven problem due to spreading depressionlike changes in subcortical areas of the brain [57] and in the brainstem [46] the vestibular episodes with or without additional brainstem signs described here might be a form of brainstem aura. This mechanism of neuronal dysfunction induces a release of neuropeptides from sensory neurons, which leads to a sterile inflammation of dural blood vessels with extravasation of plasma proteins causing, on the one hand, headache, and, on the other, an increase in regional blood flow in the brainstem, cingulate, auditory, and visual association cortices during migraine without aura [61] or a decrease in regional blood flow in the basilar artery territory and the temporal and occipital cortices during basilar migraine (hexamethyl propyleneamine oxime single photon emission computed tomography, HMPAO Spect [54]). Decrease in regional blood flow in migraine attacks, particularly in basilar migraine, can occasionally cause ischemic infarcts. The frequency of migrainous infarcts was reported to be as high as about 4% by Sturzenegger and Meienberg [58] and 2.2% in our study.

Ocular motor abnormalities in the symptom-free interval may reflect subtle continuous neuronal dysfunction in certain brainstem nuclei, as shown by the persisting brainstem activation on positron-emission tomography. These ocular motor deficits are not typical late (cumulative) ischemic sequelae of migraine, for they can be observed in young patients presenting after their first attacks. This was reported earlier in the literature [23], and we have confirmed the observation in our younger patients with vestibular migraine. The combination of recurrent episodic vertigo and ocular motor abnormalities in the symptom-free interval recalls familial episodic ataxias, which have been recently identified as channelopathies. Episodic ataxia type 1 is due to a missense point mutation in the potassium channel gene (*KCNA1*) on chromosome 12p [34]. Patients with another form of episodic ataxia (type 2) generally show interictal nystagmus and headache [29] and often develop progressive ataxia and dysarthria with cerebellar vermian atrophy. This latter disorder has recently been localized to

chromosome 19p [60] and is combined with familial hemiplegic migraine, which is also linked to chromosome 19 [48]. About one-half of the affected individuals of four families with familial episodic ataxia associated with chromosome 19p had migraine headaches, and several had episodes typical of basilar migraine [4]. In episodic ataxia type 2, an abnormally elevated pH level in the cerebellum was measured by magnetic resonance spectroscopy. The attacks of these patients – as in some other channelopathies – respond to acetazolamide [3, 4]. By analogy, one could speculate that brainstem deficits in the symptom-free interval of vestibular migraine reflect an electrophysiological neuronal membrane instability in one of the ion channels (sodium, calcium, chloride, potassium) known to be involved in the pathomechanism of other inherited disorders with *episodic* neuronal dysfunction [11, 50, 51].

Origin of vertigo in migraine

The vestibular system includes the peripheral labyrinths, eighth nerves, and central pathways extending from the vestibular nuclei to the vestibulo-cerebellum and through ascending fibers (such as the medial longitudinal fasciculus) to the oculomotor nuclei and the supranuclear integration centers in the rostral midbrain, the vestibular thalamus, and its cortical projections [9, 10]. Consequently, vertigo may arise from a lesion or inadequate stimulation of peripheral or central vestibular structures encompassing the brainstem, the thalamus, or the parietoinsular vestibular cortex. The regular association of vertigo with central ocular motility disturbances (Table 4) strongly suggests that both arise from brainstem dysfunction involving the vestibular nuclei in cases of rotational vertigo and spontaneous nystagmus [10]. Transient brainstem dysfunction has been shown by significant alterations in brainstem auditory evoked potentials in the pontomesencephalic brainstem (prolonged interwave III–V interval) during basilar migraine attacks; this condition returned to normal on clinical recovery [30, 62].

Other authors have found a surprisingly high frequency of peripheral audiovestibular deficits, more than 29% of which were related to the attacks [39], and also occurred in the symptom-free interval in 21% [12]. They argued that a unilateral hyporesponsiveness on caloric testing confirms the existence of peripheral dysfunction in some patients diagnosed as having basilar migraine [23, 39]. However, lacunar infarctions and small demyelinating plaques involving the root entry zone of the eighth nerve and/or the vestibular nuclei can mimic peripheral vestibular disease. In such cases rotational vertigo and spontaneous nystagmus are combined with the reduction in or absence of caloric responses on the affected side [17, 36]. Furthermore, differences in the frequency of peripheral signs and symptoms in basilar migraine can be partly explained by the different definitions of “a vestibular canal paresis” on caloric testing; this was based on side asymmetries, either of more than 22% [12] or of more than 30% in our study.

Nevertheless, temporary or permanent peripheral vestibular and auditory deficits can be found in some patients with basilar migraine; some are indistinguishable from signs and symptoms of peripheral labyrinthine disease [35]. In these patients the involvement of the labyrinth itself may be causative secondarily to the basilar migraine-induced decrease in regional blood flow of the inner ear. The inner ear is supplied by the anterior inferior cerebellar artery through the internal auditory artery (branching in common cochlear and anterior vestibular arteries). The anterior inferior cerebellar artery arises from the basilar artery and also supplies the anterolateral pons, middle cerebellar peduncle, and cerebellar flocculus [40]. A definitive clinical classification of the lesion site, however, is not possible in individual patients with labyrinthine, vestibular nerve, or vestibular nucleus dysfunction.

A theoretically conceivable combination of central and peripheral audiovestibular dysfunction in a basilar migraine attack is plausible in some cases. Such a combination is supported by the distribution of neuro-otological signs during the attack; these signs were classified as being of central origin in 14%, peripheral in 7.5%, and indeterminate in 17.5% [39]. If the above infratentorial anatomical structures are affected in basilar migraine, the disease can mimick other peripheral labyrinthine diseases such as Menière’s disease, thus posing problems for the differential diagnosis. This would explain the significant difference in the prevalence of migraine in “classical” (22%) and “vestibular” (81%) Menière’s disease and underline the different etiologies of the two conditions [52]. A correct diagnosis can be established only by the time course, family history, additional central ocular motor signs, and especially the efficacy of appropriate treatment.

A distressing (in particular, rotational) vertigo is atypical of supratentorial vestibular thalamic and cortical lesions unless it occurs in unique ischemic events [7] or in vestibular epilepsy arising from the superior temporal lobe [27, 49].

Overall, it is most likely that vertigo in basilar migraine and vestibular migraine are due to a functional vestibular tone imbalance caused by an asymmetric activation or deactivation of bilateral vestibular neuronal activity during the attack. This may predominantly involve vestibular brainstem structures extending from the pontomedullary vestibular nuclei (inducing rotational vertigo) to the rostral midbrain tegmentum (inducing ocular motor dysfunction). It corresponds best to the asymmetric activation of the entire pontomesencephalic brainstem structures found on positron-emission tomography [61].

Acknowledgements We thank Mrs. C. Frenzel and Mrs M. Rindle for orthoptic assistance and are grateful to Mrs. Judy Benson for critical reading of the manuscript. This work was supported by the Wilhelm Sander-Stiftung and the Deutsche Forschungsgemeinschaft (Klinische Forschergruppe Br 639/5-3).

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