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Original Research

Purkinje cells of vestibulocerebellum play an important role in acute vestibular migraine

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Both the central and peripheral vestibular systems contribute to the pathogenesis of vestibular migraine, although the mechanism of vestibular migraine remains unclear. To assess central and peripheral vestibular system damage in vestibular migraine and explore the underlying mechanism we performed vestibular function tests, including a caloric test, spontaneous, gaze-evoked nystagmus and saccadic, pursuit and optokinetic eye movements to evaluate the involvement of the central and/or peripheral vestibular system in subjects with acute vestibular migraine episodes. It was found that both peripheral and central vestibular systems were damaged in vestibular migraine patients with the number of subjects with central deficits significantly larger than those with peripheral deficits. The cerebellum, especially the vestibule cerebellum, is the most important part of the central vestibular system. Loccullus and paraflocculus are essential structures of cerebellar circuitry controlling vestibular nuclei and oculomotor functions and are anatomically linked with the "migraine pathway". Purkinje cells are the only source of cerebellar output and it innervates inhibitory action. Therefore, we examined the effect of the electric stimulation on paraflocculus Purkinje cells by using a specific electrical stimulation of trigeminal ganglia to induce a migraine-like phenomenon in animal part. Moreover, electrophysiological recordings showed that paraflocular Purkinje cells of rats underwent electrical stimulation of trigeminal ganglia resulted in partial inhibition. It is suggested that Purkinje cells in the paraflocculus could be inhibited after the occurrence of migraine episode and this inhibition may be an important factor leading to vestibular migraine.

Keywords

Vestibular migraine; vestibular function; Purkinje cells; paraflocculus; whole-cell recording patch clamping

1. Introduction

Migraine and vertigo are two common neurological diseases. Epidemiological studies have shown that the prevalence of migraine in the vertigo population is far greater than that of the general population, and so is the prevalence of vertigo in the migraine population (Akdal et al., 2015; Teggi et al., 2016; Teixido et al., 2017). The incidence of migraine and vertigo in the general population is 16% and 7%, respectively. Thus, it can be predicted that the co-incidence of migraine and vertigo should be around 1.1%. However, the actual co-incidence of migraine and vertigo is 3.2% (Lempert and Neuhauser, 2009). The link between migraine and dizziness was first described by Edward Liveing in 1873 (Liveing, 1873). And during the last three decades, systematic studies of vertigo caused by migraines have received much attention. Various synonyms have been used to describe the combination of migraine and vestibular symptoms including, benign recurrent vertigo, migrainous vertigo, migraine-associated vertigo, migraine-related vestibulopathy and vestibular migraine (VM), vertiginous migraine and migraine-associated balance disturbance. The diagnostic criteria for VM were published in the third edition of the ICHD (ICHD-3) in 2013, indicating that VM is widely recognized in the field of vestibular headache (Olesen et al., 2013).

VM is a common recurrent vertigo attack. The main clinical findings are recurrent vertigo, motion intolerance, and other migraine symptoms that severely degrade the quality of life. It is of great clinical significance to explore its etiology and mechanism. The pathogenesis of VM is still unclear, but both the central and peripheral vestibule may participate. Dieterich and Brandt reported that 66% of vestibular migraine patients exhibited central vestibular nystagmus and abnormal saccades and/or pursuits, gaze-evoked nystagmus, and positional nystagmus (Dieterich and Brandt, 1999). Von Brevern recorded the results of oculographic findings during the acute attack and found that 50% of patients had central vestibular nystagmus, while 15% exhibited peripheral vestibular nystagmus (Von Brevern et al., 2004). Shin et al. (2014) used 18F-fluorodeoxyglucose positron-emission tomography to demonstrate that temporal-parietal-insular areas, bilateral thalami and bilateral cerebellum were activated during VM episodes . Raphe nuclei and locus coeruleus are involved in the projections of both vestibular and trigeminal pathways, and both vestibular nuclei and the trigeminal spinal tract nucleus are closely related (Espinosa-Sanchez and Lopez-Escamez, 2015).

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Thus, when the trigeminal nerve pathway is activated during a migraine attack, the central components of the vestibular system may be simultaneously activated. Additionally, the inner ear may also participate in VM occurrence, and animal experiments have shown that chemical or electrical stimulation of the trigeminal pathway accelerates blood flow in the inner ear, increases vascular permeability and plasma protein extravasation (Koo and Balaban, 2006; Vass et al., 2001).

In this study, the involvement of central and/or peripheral vestibular systems was evaluated clinically by observing nystagmus in patients with acute VM attacks. In animal experiments, electrical stimulation of trigeminal ganglia of the rat was established as a model of an acute migraine episode, and the firing of Purkinje cells in paraflocculus was recorded by use of whole-cell patch-clamp in a study that may provide a theoretical basis for future targeted therapy and prevention of VM.

2. Methods

2.1 Subjects and clinical study

A total of 178 subjects who presented at the Neurology Outpatient Clinic of Chang zheng Hospital from September 1, 2015, to May 1, 2018, were involved in this trial. Eighty-eight were assigned to the VM subject group and 90 to a control group. VM subjects met the following requirements for the diagnosis of "definite" VM according to the Lempert Olesen criteria and ICHD-3β. A: At least five episodes of moderate to severe vestibular symptoms lasting from five minutes to 72 hours. B: History of migraine with or without aura, consistent with ICHD diagnostic criteria. C: One or more of the following in at least half of the vestibular attacks: (1) At least two characteristics of migraine including: unilateral, pulsatile, moderate to severe, aggravated by daily physical activity, (2) Photophobia and phobia, (3) Visual aura, D: Other vestibular diseases, or other ICHD diagnoses were excluded (Lempert et al., 2012; Olesen et al., 2013).

Age- and sex-matched healthy volunteers without migraine or vertigo history served as the control group. Exclusion criteria for both groups were: noncooperation, otological disease, receipt of ototoxic drug therapy, central nervous disease, and other types of migraine. All subjects were advised not to take sedative drugs 24 hours before the examination. Basic data collection included age, gender, and history of motion sickness. All subjects underwent detailed neurological and vestibular examinations during an acute attack. Chartr200 VNG was used for caloric testing, with or without fixed spontaneous nystagmus, gaze-evoked nystagmus, saccadic, pursuit, and optokinetic eye movements. Chartr EP 200 was used to test both the cervical vestibular evoked myogenic potential (C-VEMP) and the ocular vestibular evoked myogenic potential (O-VEMP). The clinical protocol of the study was approved by the Ethics Committee of Changzheng Hospital, Naval Medical University (Shanghai, P. R. China). Before the experiment, subjects were fully informed of the purpose, processes, possible risks, and benefits of the study, and each participant signed an informed consent form.

Definition of pathological nystagmus: Spontaneous nystagmus with slow phase velocity $> 3^{\circ}$/s and gaze-evoked nystagmus $> 6^{\circ}$/s was considered significant. The caloric test was considered abnormal if the unilateral weakness was $> 25\%$. VEMPs interaural amplitude was considered abnormal if the asymmetry ratio was $> 40\%$.

Diagnostic criteria for peripheral vestibular system lesions included: (1) Abnormal caloric test, C-VEMP, or O-VEMP. (2) Fixation inhibition (+): Slow-phase velocity of spontaneous nystagmus was reduced by more than 50% with fixation. (3) No sign of central nervous system involvement. Subjects were only diagnosed after these criteria were satisfied.

Diagnostic criteria for central vestibular system lesions included: (1) Ocular motor abnormalities: impairments of gaze-evoked nystagmus or impaired saccadic or impaired pursuit or impaired optokinetic nystagmus; (2) Fixation inhibition (-): Slow-phase velocity of spontaneous nystagmus reduced less than 50% with fixation. The diagnosis was made after at least one criterion was satisfied.

2.2 Electrical stimulation of trigeminal ganglia

An acute migraine model was established by electrical stimulation of the rat trigeminal ganglia as previously described (Limmroth et al., 2001; Lu et al., 2016; Zhang et al., 2013). Male Sprague-Dawley rats (18 days old) were anesthetized with 10% chloralhydrate (4 ml/kg, intraperitoneally) and fixed in a stereotaxic frame. A 3 mm diameter hole was drilled (3.3 mm posterior to the bregma and 3 mm from the sagittal suture) to expose the dura mater, and stimulating electrodes were inserted into the right trigeminal ganglion (depth 9.2-9.8 mm below the dura). The trigeminal ganglion was electrically stimulated for 10 minutes (1.0 mA, 5 ms, 5 Hz). The model was confirmed by electrically stimulated contraction of the ipsilateral masseter muscle and increased oral and nasal secretions. In the sham group, electrodes were inserted for 10 minutes without electrical stimulation.

2.3 Preparation of paraflocculus slices and whole-cell recording

Rats were decapitated immediately after the electrical stimulation of trigeminal ganglia. The experimental procedures conformed to the Naval Medical University guidelines on the ethical use of animals, and the pain was minimized. The brain was quickly removed and immersed in the ice-cold artificial cerebrospinal fluid. A block of tissue containing the cerebellum was cut and fixed on a vibratome (Leica VT1200S, Germany). Serial coronal slices (250 μm) were cut and transferred to ACSF containing 126 mM NaCl, 2.5 mM KCl, 1.25 mM NaH_2PO_4, 2 mM $MgSO_4$, 2.5 mM $CaCl_2$, 25 mM $NaHCO_3$ and 10 mM glucose at 32 °C. Slices were incubated for at least one hour before patch-clamp recording (Wang and Zheng, 2001).

Purkinje cells were visualized with an upright microscope (BX50WI, Olympus) using infrared differential interference contrast optics. Whole-cell current-clamp recordings were made using an EPC10 amplifier and PatchMaster 2.54 software (HEKA, Germany). Electrodes had a resistance of 3-4 MΩ when filled with the patch pipette solution (130 mM K-gluconate, 8 mM NaCl, 0.1 mM $CaCl_2$, 0.6 mM EGTA, 2 mM ATP-Mg, 0.1 mM GTP-Na_3 and 10 mM HEPES, pH: 7.4). Artificial cerebrospinal fluids, including 95% O_2 and 5% CO_2, were circulated during the recording at 2 ml/minute. Spontaneous Purkinje cell firing was recorded under the current clamp. All cells from the different slices and cells within each group were obtained from at least six animals. Data were analyzed with pClamp and Origin (Microcal Software).

2.4 Statistical analysis

SPSS 21.0 was used for statistical analysis. *t*-tests or rank-sum tests were used to analyze measurement data, and a chi-square test was used to analyze enumerated data. Measurement data were reported as mean ± SE. Values of $P \leq 0.05$ were considered statistically significant.

3. Results

3.1 Clinical characteristics of VM and control subjects

As shown in Table 1, the VM group included 88 diagnosed subjects (13 males and 75 females) aged 13-54 years (mean age 34.4 ± 0.88 years). The control group comprised 16 males and 74 females aged 14-56 years (mean age 32.9 ± 0.68 years). There were no statistical differences between groups for gender and age. However, a family history of migraine and motion sickness of VM subjects was much higher than in the control group ($P < 0.05$). In the VM group, 47 subjects were characterized as having vertigo, including 18 cases of spontaneous vertigo (vertigo without any cause), 22 cases of positional vertigo (vertigo evoked by change of position), and 7 cases of visually induced vertigo (vertigo triggered by a complex or large moving visual stimulus) and 41 subjects had motion intolerance (dizziness with nausea evoked by head movement).

3.2 Vestibular function of VM and control subjects

The vestibular function of subjects is listed in Table 2. Impaired caloric testing, C-VEMP, O-VEMP, nystagmus, saccadic, pursuit inaccuracy, impaired optokinetic nystagmus, and gaze-evoked nystagmus of the VM group was significantly greater than for the control group ($P < 0.05$). The diagnosis of central and peripheral vestibular system lesions was described in the Method section 2.1. Fig. 1 shows the number of central and peripheral vestibular lesions of VM and control subjects.

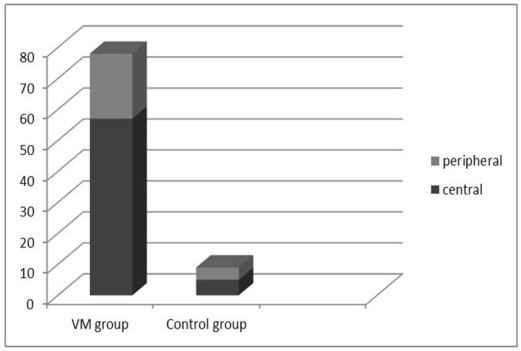

Figure 1. The number of central and peripheral vestibular lesions of VM and control subjects. 57 subjects in the VM group and 5 subjects in the control group showed evidence of the central deficit. 21 subjects in the VM group and 4 subjects in the control group showed evidence of peripheral deficit.

3.3 Central and peripheral vestibular lesions of VM and control subjects

This study included 88 VM subjects, of whom 49 presented a central vestibular system deficit, 13 presented peripheral vestibular system deficit, and 8 presented both central and peripheral system deficits. In the control group, 5 subjects showed central system deficit, 4 subjects showed peripheral system deficit, and no subject exhibited both deficits. As shown in Fig. 1, 57 (49 + 8) subjects in the VM group and 5 subjects in the control group showed a central deficit, and 21 (13 + 8) subjects in the VM group and 4 subjects in the control group showed a peripheral deficit. The central and peripheral deficits of the VM group were significantly larger in the control group ($P < 0.05$). Unsurprisingly, the central deficit (64.8%) was significantly greater than the peripheral deficit (23.8%) in the VM group.

Table 1. Clinical characteristics of VM patients and control subjects

	VM group (n = 88)	Control group (n = 90)	*P* value
Sex			
male	13	16	0.587
female	75	74	
Age (years)	34.4 ± 0.88	32.9 ± 0.68	0.184
Family history	68	11	< 0.001
Motion sickness	59	12	< 0.001
Vestibular findings			
Spontaneous vertigo	18	-	-
Positional vertigo	22	-	-
Visual evoked vertigo	7	-	-
Motion intolerance	41	-	-

Mean values ± SE are reported for measurement data. Family history: Family history of migraine; Spontaneous vertigo: vertigo without any cause; Positional vertigo: vertigo evoked by the change of position; Visual evoked vertigo: vertigo evoked by visual stimuli; Motion intolerance: dizziness with nausea evoked by head movement.

3.4 Purkinje cell firing

As shown in Fig. 2, the average Purkinje cell firing in the ipsilateral to electrode in the sham (IS) group, the contralateral to electrode in the sham (CS) group, the ipsilateral to electrode in the electrical (IE) stimulation group and the contralateral to electrode in the electrical (CE) stimulation group were 30.23 ± 5.95, 31.14 ± 4.82, 15.57 ± 3.14 and 17.03 ± 3.27 Hz, respectively. In either the sham or electrical stimulation groups, there was no significant difference in the firing of Purkinje cell between the ipsilateral and contralateral electrodes ($P = 0.913$ IS group vs. CS group; $P = 0.756$ IE group vs. CE group). However, the firing of Purkinje cells on both sides in the electrical stimulation group was much lower than that of the sham group ($P = 0.040$ IS group vs. IE group; $P = 0.027$ CS group vs. CE group).

4. Discussion

The pathogenesis of VM has been unclear until now, and it is not even clear whether its source derives from the central or the peripheral vestibular system. In this study, the vestibular and oculomotor function was explored through a variety of vestibular function tests in subjects with acute vestibular migraine episodes. 57 VM subjects (64.8%) presented with a central vestibular system deficit, and 21 VM subjects (23.8%) showed a peripheral vestibu-

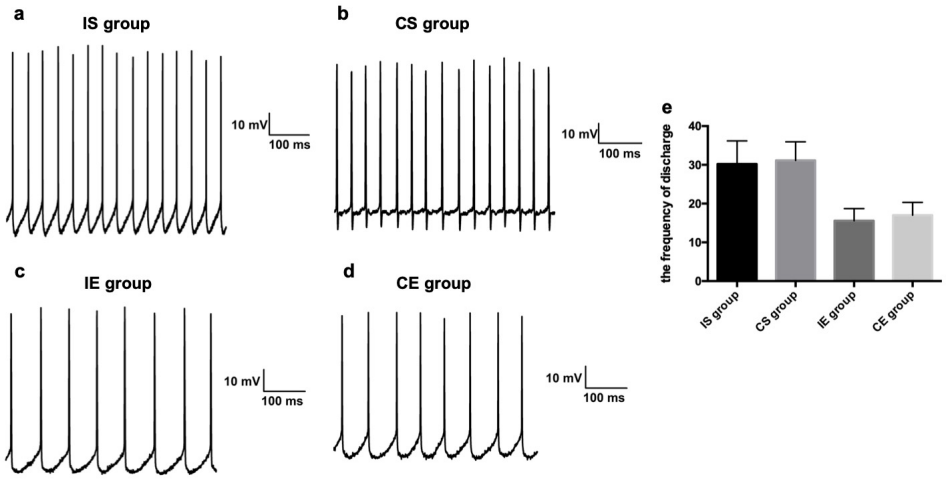

Figure 2. Purkinje cell firing. a: Ipsilateral to sham group electrode (IS group). b: Contralateral to sham group electrode in (CS group). c: Ipsilateral to the electrical stimulation group electrode (IE group). d: Contralateral to electrical stimulation group electrode (CE group). e: The average firing rate of Purkinje cells in IS, CS, IE, and CE groups. (*$P < 0.05$, $P = 0.04$ IS group vs. IE group, $P = 0.03$ CS group vs. CE group).

Table 2. The vestibular function of VM patients and control subjects

	VM group (n = 88)	Control group (n = 90)	P value
Impaired caloric testing	17	3	0.002*
Impaired C-VEMP	15	2	0.002*
Impaired O-VEMP	14	2	0.003*
Nystagmus	32	2	< 0.001*
Saccadic inaccuracy	28	3	< 0.001*
Pursuit inaccuracy	24	2	< 0.001*
Impaired optokinetic nystagmus	42	4	< 0.001*
Gaze-evoked nystagmus	17	3	0.002*

C-VEMP: cervical vestibular evoked myogenic potential; O-VEMP: ocular vestibular evoked myogenic potential; Nystagmus: spontaneous nystagmus; *VM group compared to controls when $P < 0.05$.

lar system deficit. These results indicate that both peripheral and central vestibular systems contributed to vestibular migraine and that the role of the central pathway seemed to dominate. Since the flocculus and paraflocculus are the essential structures of cerebellar circuits that control vestibular nuclei and oculomotor functions and they are anatomically linked with the "migraine pathway", the effect of electrical stimulation on these structures in the rat was examined by specifically stimulating the trigeminal ganglia to induce a migraine-like phenomenon. It was found that in response to this stimulation, parafollicular Purkinje cells in the trigeminal ganglia became partially inhibited. It is suggested that Purkinje cells in the paraflocculus can become inhibited following an episode of migraine. This inhibition may be an important factor leading to vestibular migraine.

The cerebellum, especially the vestibulocerebellum, is the most important part of the central vestibular system. It controls muscle balance and the coordination of eye, body, and head movement. The involvement of the flocculonodular lobe provides a good fit for various kinds of central gaze-induced, and down-jump nystagmus, abnormal scan and tracking motion, and vestibulo-ocular reflex and failure of gaze suppression in VM subjects. Shin et al. demonstrated by positron emission computed tomography that bilateral cerebellum activation was most significant during the onset of VM (Shin et al., 2014).

Previous studies have shown that cerebellar inhibition is reduced in migraineurs, but the mechanism remains obscure (Brighina et al., 2009; Mehnert and May, 2019). In the animal studies reported here, an acute migraine model was established by electrically stimulating the trigeminal ganglia in the rat. The firing of Purkinje cells was observed in the parafollicular slice using a patch-clamp recording. As expected, the firing of Purkinje cells on both sides of the electrical stimulation group was much lower than the sham group. Purkinje cells are the only source of cerebellar output, and they innervate an inhibitory effect. The decreased inhibitory output of Purkinje cells may cause the loss of the inhibitory effect of GABA in vestibular nuclei and facilitate the onset of vestibular symptoms.

Above all, it was hypothesizedthat vestibulocerebellar involvement in migraine might be a potential mechanism of VM. The results reported here also support the conclusion that there was no significant difference in Purkinje cell firing rate between the ipsilateral and contralateral electrodes in either the sham or electrostimulation group. Although the electrically-induced migraine model is known, the effectiveness of this model in mimicking the possible impact of migraine episodes on the activity of Purkinje cells must be determined. To verify this conclusion, a chronic migraine model in rats is also being established by the infusion of an inflammatory soup through a cannula on the dura.

Calcium channels play an important role in the pathogenesis of migraine and are highly expressed in Purkinje cells, providing a fundamental basis to the Purkinje cells intrinsic firing (Vincent and Hadjikhani, 2007). The defective calcium channels in migraine patients may be a cause of reduced Purkinje cell inhibition.

In this clinical study, 75 female and 13 male subjects were diagnosed with VM, of which 77.3% (68 subjects) had a family history of migraine. A total of 67% of subjects had a history of motion sickness. This is consistent with previous reports (Golding, 1998; Johnson, 1998; Kayan and Hood, 1984; Marcus et al., 2005). VM is closely related to motion sickness, with vestibular symptoms being the main clinical manifestation. Possible mechanisms include: (i) Abnormal integration of semicircular canal and otolith system activity in patients with vestibular migraine; (ii) Symptoms such as nausea, dizziness, and headache of VM and motion sickness may share the same brainstem neural circuit; (iii) There are extensive connections between the caudal part of the trigeminal spinal tract nucleus and the vestibular nuclei (Cuomo-Granston and Drummond, 2010; Diagne et al., 2006; Lewis et al., 2011; Wang and Lewis, 2016).

A total of 47 out of 88 migraine subjects developed vertigo symptoms, including spontaneous, positional, and visually evoked vertigo, and 41 subjects showed motor intolerance. Overall, 30 of 47 subjects with vertigo and 27 of 41 subjects with motor intolerance showed central vestibular system deficit, and 19 of 47 subjects with vertigo and 2 of 41 subjects with motor intolerance showed peripheral vestibular system deficit. Analysis of vestibular function found no significant difference in the central vestibular system lesion between the two groups, whereas a peripheral vestibular system lesion in the subjects with vertigo was much greater than for patients with motor intolerance. Therefore, it was hypothesized that both peripheral and central vestibular systems were involved in the occurrence of vestibular migraine. The involvement of the central vestibular system lays the foundation for vestibular symptoms, and the involvement of the peripheral vestibular system plays an important role in the occurrence of vertigo.

5. Conclusion

The vestibular and oculomotor function was explored through a variety of vestibular function tests in subjects with acute vestibular migraine episodes. It was concluded that both peripheral and central vestibular systems might contribute to vestibular migraine and that the contribution of the central pathway seemed to predominate. The effect of electrical stimulation on parafollicular Purkinje cells was examined by using stimulation of trigeminal ganglia to induce a migraine-like phenomenon in rats. It was found that parafollicular Purkinje cells of the trigeminal ganglia that underwent such electrical stimulation were partial inhibited. It is suggested that Purkinje cells in the paraflocculus could be inhibited after the occurrence of a migraine episode and that this inhibition may be an important factor leading to vestibular migraine.

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Conflict of interest

The authors declare no competing interests.

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References

Akdal, G., Baykan, B., ErtaŞ, M., ZarifoĞlu, M., Karli, N., Saip, S. and Siva, A. (2015) Population-based study of vestibular symptoms in migraineurs. *Acta Oto-laryngologica* **135**, 435-439.

Brighina, F., Palermo, A., Panetta, M. L., Daniele, O., Aloisio, A., Cosentino, G. and Fierro, B. (2009) Reduced cerebellar inhibition in migraine with aura: a TMS study. *The Cerebellum* **8**, 260-266.

Cuomo-Granston, A. and Drummond, P. D. (2010) Migraine and motion sickness: what is the link? *Progress in Neurobiology* **91**, 300-312.

Diagne, M., Valla, J., Delfini, C., Buisseret-Delmas, C. and Buisseret, P. (2006) Trigeminovestibular and trigeminospinal pathways in rats: retrograde tracing compared with glutamic acid decarboxylase and glutamate immunohistochemistry. *Journal of Comparative Neurology* **496**, 759-772.

Dieterich, M. and Brandt, T. (1999) Episodic vertigo related to migraine (90 cases): vestibular migraine? *Journal of Neurology* **246**, 883-892.

Espinosa-Sanchez, J. M. and Lopez-Escamez, J. A. (2015) New insights into pathophysiology of vestibular migraine. *Frontiers in Neurology* **6**, 12.

Golding, J. F. (1998) Motion sickness susceptibility questionnaire revised and its relationship to other forms of sickness. *Brain Research Bulletin* **47**, 507-516.

Johnson, G. D. (1998) Medical management of migraine-related dizziness and vertigo. *The Laryngoscope* **108**, 1-28.

Kayan, A. and Hood, J. D. (1984) Neuro-otological manifestations of migraine. *Brain* **107**, 1123-1142.

Koo, J. W. and Balaban, C. D. (2006) Serotonin-induced plasma extravasation in the murine inner ear: possible mechanism of migraine-associated inner ear dysfunction. *Cephalalgia* **26**, 1310-1319.

Lempert, T. and Neuhauser, H. (2009) Epidemiology of vertigo, migraine and vestibular migraine. *Journal of Neurology* **256**, 333-338.

Lempert, T., Olesen, J., Furman, J., Waterston, J., Seemungal, B., Carey, J., Bisdorff, A., Versino, M., Evers, S. and Newman-Toker, D. (2012) Vestibular migraine: diagnostic criteria. *Journal of Vestibular Research* **22**, 167-172.

Lewis, R. F., Priesol, A. J., Nicoucar, K., Lim, K. and Merfeld, D. M. (2011) Abnormal motion perception in vestibular migraine. *The Laryngoscope* **121**, 1124.

Limmroth, V., Katsarava, Z., Liedert, B., Guehring, H., Schmitz, K., Diener, H. C. and Michel, M. C. (2001) An *in vivo* rat model to study calcitonin gene related peptide release following activation of the trigeminal vascular system. *Pain* **92**, 101-106.

Liveing, E. (1873) On megrim, sick-Headache, and some allied disorders, a contribution to the pathology of nerve-storms. *Kessinger Publishing* , Whitefish, MT.

Lu, W., Li, B., Chen, J., Su, Y., Dong, X., Su, X. and Gao, L. (2016) Expression of calcitonin gene-related peptide, adenosine A2a receptor and adenosine A1 receptor in experiment rat migraine models. *Biomedical Reports* **4**, 379-383.

Marcus, D. A., Furman, J. M. and Balaban, C. D. (2005) Motion sickness in migraine sufferers. *Expert Opinion on Pharmacotherapy* **6**, 2691-2697.

Mehnert, J. and May, A. (2019) Functional and structural alterations in the migraine cerebellum. *Journal of Cerebral Blood Flow & Metabolism* **39**, 730-739.

Olesen, J., Bes, A., Kunkel, R., Lance, J. W., Nappi, G., Pfaffenrath, V. and other committees of Headache Classification Committee of the International Headache Society (IHS) (2013) The international classification of headache disorders, (beta version). *Cephalalgia* **33**, 629-808.

Shin, J. H., Kim, Y. K., Kim, H. J. and Kim, J. S. (2014) Altered brain metabolism in vestibular migraine: comparison of interictal and ictal findings. *Cephalalgia* **34**, 58-67.

Teggi, R., Manfrin, M., Balzanelli, C., Gatti, O., Mura, F., Quaglieri, S., Pilolli, F., Redaelli de Zinis, L. O., Benazzso, M. and Bussi, M. (2016) Point prevalence of vertigo and dizziness in a sample of 2672 subjects and correlation with headaches. *Acta Otorhinolaryngologica Italica* **36**, 215-219.

Teixido, M., Baker, A. and Isildak, H. (2017) Migraine and benign paroxysmal positional vertigo: A single-institution review. *The Journal of Laryngology & Otology* **131**, 508-513.

Vass, Z., Steyger, P. S., Hordichok, A. J., Trune, D. R., Jancso, G. and Nuttall, A. L. (2001) Capsaicin stimulation of the cochlea and electric stimulation of the trigeminal ganglion mediate vascular permeability in cochlear and vertebro-basilar arteries: a potential cause of inner ear dysfunction in headache. *Neuroscience* **103**, 189-201.

Vincent, M. and Hadjikhani, N. (2007) The cerebellum and migraine. *Headache: The Journal of Head and Face Pain* **47**, 820-833.

Von Brevern, M., Zeise, D., Neuhauser, H., Clarke, A. H. and Lempert, T. (2004) Acute migrainous vertigo: clinical and oculographic findings. *Brain* **128**, 365-374.

Wang, J. and Lewis, R. F. (2016) Contribution of intravestibular sensory conflict to motion sickness and dizziness in migraine disorders. *Journal of Neurophysiology* **116**, 1586-1591.

Wang, Z. and Zheng, P. (2001) Characterization of spontaneous excitatory synaptic currents in pyramidal cells of rat prelimbic cortex. *Brain Research* **901**, 303-313.

Zhang, Y., Shao, G., Zhang, W., Li, S., Niu, J., Hu, D., Yang, M. and Ji, X. (2013) Gabapentin inhibits central sensitization during migraine. *Neural Regeneration Research* **8**, 3003.