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Letter to the Editor

Migraine-related vertigo: The challenge of the basic sciences

The author comments on migraine-related vertigo (MRV) and shares his views on migraine pathophysiology in general. The pathophysiology of migraine is not fully understood, but it appears that aura and headache are based on different mechanisms and they should thus be discussed separately [1].

Aura symptoms originate from the cerebral cortex but functional MRI does not support ischemia as their cause [2]. The only known disturbance that could explain the aura symptoms would be the human equivalent of cortical spreading depression, associated with initial cortical hyperperfusion followed by more prolonged hypoperfusion. The concept of a 'vulnerable cortex' has arisen, based on interictal migraine trait markers such as defective habituation to repetitive stimuli and magnetic resonance spectroscopy findings. Genetic abnormalities have been shown in familial hemiplegic migraine, but remain elusive in migraine with and without aura.

Activation and sensitization of the trigeminovascular system are the basic mechanisms of pain in migraine and are associated with neurogenic inflammation and vasodilation at the neurovascular junction. Subsequent activation and sensitization of second- and third-order neurons lead to nausea and vomiting through connections with centers such as the solitary tract nucleus. Dilation of cranial vessels is generic to cranial neurovascular activation and is probably mediated by the trigeminoparasympathetic reflex [3]. Evidence is accumulating for a primary dysfunction of brainstem nuclei (such as the dorsal raphe nucleus, locus coeruleus and periaquaductal grey) regulating antinociception and vascular control. Using the positron emission tomography technique, brainstem activation has been shown during spontaneous migraine attacks, which persisted after injection of sumatriptan and relief of headache, photophobia and phonophobia [4]. Certain prophylactic drugs, such as valproate, influence these brainstem nuclei. As the author correctly reminds us, some of the beta-blockers that have proven prophylactic effect do not pass the blood–brain barrier. However, a 'peripheral' prophylactic effect of a drug does not exclude a 'central' pathogenesis. Indeed, propranolol had no effect on nitric oxide-induced migraine, suggesting that nitric oxide induces migraine at a deeper level of the pathophysiological cascade than the prophylactic effect of propranolol [5]. Furthermore, peak headache intensity during glyceryl trinitrate infusion does not differ between migraineurs and control subjects, whereas only migraineurs experienced a delayed headache, indicating that simple vasodilation is not the only event responsible for migraine headache [6].

MRV can be discussed in view of these pathophysiological considerations:

1. Is MRV a migraine aura phenomenon?

   It is tempting to consider MRV as an aura since the vertigo may not be accompanied by headache. MRV does however often lack the duration characteristics and the gradual development of a typical migraine aura. Nevertheless, two possible mechanisms may relate vertigo to migraine aura. Firstly, vertigo might be a 'brainstem aura'. Alternatively, connections from the posterior parietal cortex to the vestibular nuclei may provide a direct link between cortical aura mechanisms and areas important for vestibular information processing. In MRV, the diagnostic criteria for basilar migraine are not fulfilled as they require at least two aura symptoms from the posterior circulation territory [7]. Hence, several groups have proposed separate diagnostic criteria for MRV, including ourselves [8].
2. Is the origin of MRV located at the level of central or peripheral vestibular pathways?

   Based on theoretical grounds, the dysfunction of MRV could be located at the central or peripheral vestibular level [9]. In a recent prospective study, patients were studied during an acute MRV episode [10]. It was found that vertigo presented more as a central than as a peripheral vestibular disorder, although in many cases the site of involvement could not be determined with certainty. The reciprocal connections between the vestibular nuclei and the trigeminal nucleus caudalis may provide a mechanism by which central vestibular pathways interact with the trigeminovascular system. Furthermore, the vestibular nuclei also project to monoaminergic nuclei and in turn receive monoamine and neuropeptide input. Both interactions favor a central origin of vestibular dysfunction in migraine. Subclinical cerebellar impairment has

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furthermore been demonstrated in the common subtypes of migraine [11]. The vestibular periphery however may indeed also influence migraine pathways. There is not only a significant trigeminal sensory innervation of the cristae ampullaris, but also a possibility that different agents released through activation of trigeminal and eighth nerve fibres contribute to MRV via paracrine actions on neural and vascular elements [12]. In this context, two interesting clinical observations have been made. Firstly, it has been shown that during motion sickness, induced by optokinetic stimulation, photophobia and scalp tenderness develop preferentially in migraine patients [13]. Secondly, painful trigeminal stimulation elicits a peripheral vestibular imbalance in migraine patients [14]. The suggestion that optokinetic reflex-related nystagmus could be the link between MRV and motion sickness [15] is attractive and has to be evaluated by basic and clinical research. However, it has to be stressed that peripheral stimuli may simply be the trigger for MRV and that a peripheral presentation of MRV could result from central mechanisms.

In summary, the available evidence hitherto suggests that MRV is more likely related to migraine headache mechanisms than to migraine aura. The vestibular dysfunction is probably mainly located at the level of the brainstem and possibly the cerebellum, but may be expressed as a peripheral vestibular syndrome. Finally, the watchword "towards" in the title of the review 'Migraine-related vertigo: towards a distinctive entity' seems fully justified, just as the call for concerted clinical and basic studies in the field of MRV [8]. We hope that our clinical effort will be used to motivate further hypothesis driven research and productive debate with basic sciences.

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