Summary of scientific highlights from EHMTIC 2016

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Introduction

The 5th European Headache and Migraine Trust International Congress (EHMTIC) gathered nearly 1,000 headache specialists from 69 countries for 4 days in Glasgow. The following is a short summary of the highlights from plenary lectures, symposiums and poster sessions during the congress. The posters and abstracts can be found at **http://cep.sagepub.com/content/36/1 suppl** and can be cited as Cephalalgia (2016) 36 (1 suppl) 1–185.

Sleep and migraine

The link between sleep and headache was a hot topic at this year's EHMTIC with both a plenary session and several posters focusing on the topic. Dr Phillip Holland from King's College London showed that the migraine and sleep pathways overlap in the brain, with the trigeminocervical complex (TCC) having projections to the periaqueductal grey (PAG), rostral ventromedial medulla (RVM), locus coeruleus (LC), thalamus, and hypothalamus.[1] Interestingly the hypothalamus, the master clock of sleep, also seems to be a key region in the generation of migraines.[2–5] In mice, chronic inhibition of the LC, which plays a key role in both sleep and arousal, pain processing, trigeminal nociception and migraine, led to decreased neuronal nociceptive activation in the TCC, underlining the importance of this brain region in headache. (Poster ref 121). Not only sleep, but also light and hence the circadian rhythm play a role in migraines.[6–8] Triptans both alleviate trigeminovascular pain and blunt the circadian response to light.[9] A mouse model of circadian disruption (CK1δ loss of function mutation) was found to have lower cortical spreading depression threshold and higher levels of mechanical hyperalgesia.[10]

There is a bidirectional relationship between migraine and insomnia.[11] A pilot study showed long-term reduction in headache frequency in chronic migraine patients who underwent cognitive behavioural therapy for insomnia (CBT-i).[12] Comorbid chronic pain, depression, and/or anxiety in migraine patients are associated with higher insomnia severity index scores regardless of migraine frequency and severity, hence this patient subgroup is a target for further CBT-i studies (Poster ref 188).

Sex hormones and migraine

Dr Diana Krause presented findings detailing the role of oestrogen in the trigeminovascular system and in the initiation of migraine attacks. Oestrogen binds to the oestrogen receptors (ERά) on cerebral vessels to increase the release of endothelial nitric oxide (NO), a potent vasodilator, and subsequently modulate vascular tone.[13,14] In cerebral

arteries, levels of oestrogen can determine the effects of cyclooxygenase inhibition resulting in either vasodilation or vasoconstriction.[15] Oestrogen also attenuates interleukin-1 (IL-1) induced inflammatory responses in rat cerebral blood vessels. Ovariectomised female rats that were treated with oestrogen displayed no IL-1 induced increased COX-2 arterial endothelium levels compared to ovariectomised rats not treated with oestrogen.[16] In humans, changes in oestrogen status appear to influence onset of migraine attacks. Oestrogen receptors were also found in the human trigeminal ganglion (TG) where they are co-localised with calcitonin gene-related peptide (CGRP) in 50% of examined cells.[17] In rats, decreased oestrogen levels increase CGRP expression and a normalisation of levels suppresses CGRP gene expression.[18] Both of these observations may help better explain the role of oestrogen in the development of migraine and headache.

Experimental studies in migraine

Historically, both the blood-brain-barrier (BBB) and the brainstem have been investigated in migraine. Two MRI studies of migraine with and without aura suggested that the BBB is not disrupted during spontaneous migraine attacks (Poster refs 175, 355). Findings in the brainstem of migraine patients included increased perfusion during attacks with aura (Poster ref 355), a positive correlation between 5-HT1B receptor binding and days since last attack (Poster ref 405), and structural alterations (Poster ref 172).

In a longitudinal MRI study with scans done every morning on 31 consecutive days in the same migraine patient, hypothalamic activity and functional connectivity between hypothalamus and the spinal trigeminal nuclei increased during the 24 hours preceding the next migraine attack, suggesting that hypothalamus is involved in generation of premonitory symptoms (Poster ref 201). Another fMRI study demonstrated that metoprolol might play a role in migraine prevention via a central effect in hypothalamus (Poster ref 153).

Other studies reported that nitroglycerin (Poster ref 044) and PACAP38, but not CGRP induces premonitory symptoms in migraine provocation models (Poster ref 327), suggesting different migraine inducing mechanisms of action of these substances.

CGRP and migraine

In the Jes Olesen EHF Lecture, Lars Edvinsson gave us an excellent overview of the story of CGRP from discovery to migraine therapy. In his early studies Professor Edvinsson found that activation of the trigeminovascular system led to release of CGRP in the extracerebral circulation. Later, studies showed that CGRP was increased in the jugular vein, but not the cubital vein, during migraine attacks. These studies laid the ground for the development of the first migraine specific preventative drugs, which are currently being tested. Pierangelo Geppetti from the University of Florence presented work describing the important roles of transient receptor potential cation (TRP) channels in the regulation of CGRP in the trigeminovascular system. TRPA1 or TRPV1 channel activation can lead to CGRP release, nociceptor activation, and subsequent migraine or cluster headache induction.[19] Indeed, the mechanism behind the headache tree (*Umbellularia*) is thought to involve meningeal neurogenic inflammation via a TRPA1 mediated process.[20] Antoinette Maassen van den Brink described the neurovascular effects of CGRP in cerebral vessels and the mechanism of action of triptans and gepants in terms of direct neuronal activation, vasoconstriction and

inhibition of neuropeptide release. Gepants, which inhibit actions of CGRP, display poor brain penetration and therefore are thought to exert their actions in the periphery such as dural mast cells, the trigeminal ganglion or extracerebral vessels.[21]

With several companies presenting promising data on the efficacy and safety of CGRP antibodies or CGRP receptor antagonists, studies have further underlined the hope that these drugs will be available as a preventative treatment for migraine in the near future (Poster refs 112, 397, 110, 410, 411, 412, 423). For example, monthly AMG 334 injections in episodic migraine patients is associated with a decrease in mean monthly headache days for at least the first year of treatment (Poster ref 397). Furthermore, AMG 334 does not seem to cause coronary artery vasoconstriction even during concomitant triptan use (Poster ref 122).

New players and other considerations in migraine treatment

Lasmiditan, a new 5-HT1F agonist, was shown to inhibit dural-evoked responses from the TCC in rats (Poster ref 434) and has proven efficient for acute migraine therapy in a phase III double blinded randomised trial including 2,231 patients (SAMURAI trial, CoLucid). This drug has no effect on human arteries in vitro (Poster ref 329) and the effect is thus independent of vasoconstriction and can be used in migraine patients with cardiovascular risk factors or diseases. A multidisciplinary group came up with a pilot protocol using Brainlab stereotactic system to inject Botox directly into the sphenopalatine ganglion for prophylaxis in intractable chronic migraine patients (Poster ref 358). The home Caloric Vestibular Stimulation Device is associated with a decrease in headache frequency in episodic migraine patients by administering time-varying thermal waveforms to patients' ear canals to induce oscillations in the pulsatility index and heart rate in the B wave frequency (Poster ref 218). In chronic migraine, discontinuation of opioids results in decreased headache frequency and severity (Poster ref 217), underlining the importance of not prescribing these drugs for migraine treatment. This issue was also emphasised by Hans-Christoph Diener in his EHF Special Award lecture. A biochemical study on chronic migraine suggested that adipocytokines, which mediates inflammation, are involved in migraine chronification (Poster ref 183). The effect of Botox in treatment of chronic migraine was confirmed in several reports (Poster refs 143, 159, 231, 370).

Cluster headache

This year's winner of the Giuseppe Nappi cluster award, Shuu-Jiun Wang reported that cluster headache (CH) patients have altered functional connectivity between hypothalamus and cortical and cerebellar regions (Giuseppe Nappi Cluster Lecture). Other studies showed that the main sleep disturbance in CH patients lies in the ultraradian periodicity (most cluster attacks occur during non-rapid eye movement sleep), not in the circadian rhythm. An association between a single nucleotide polymorphism in the CLOCK gene, a basic driving force for circadian rhythms, and CH was found in a Swedish population (Poster ref 256). It is best to give CH patients melatonin to compensate for their impaired melatonin nocturnal secretion hours before their sleep midpoint as even small doses of melatonin cause significant phase shifts. Male CH patients have a higher prevalence of negative lifestyle factors compared to both female CH patients and controls. This increases the risk of comorbidities which could restrict treatment opportunities (Poster ref 141). Different possible

treatments for CH were presented, including vagal nerve stimulation (Poster ref 369), botox (Poster ref 226), and SPG stimulation (Poster refs 299, 306, 308, 312, 313).

Headaches attributed to pituitary disease

Marta Korbonits from Queen Mary University of London and Miles Levy from Leicester Medical School gave two interesting talks on endocrine disorders and headache, a highly relevant topic as up to 40% of pituitary adenoma patients suffer from headaches.[22] However, the size of the pituitary adenomas does not seem to be associated with headaches, which puts the traditional thought that headaches attributed to pituitary disease originate from a structural issue of dural extension into question. In addition, the studies on headache and cavernous sinus invasion by pituitary tumours are conflicting. Another theory is that the headaches are caused by secretion of a neuropeptide affecting the trigeminal vascular system or a paracrine diffusion from the hypothalamus. Many inflammatory peptides are found in the pituitary including substance P, CGRP, NPY, VIP, and PA-CAP, but no association with headaches attributed to pituitary disease has been found yet. Lanreotide and octreotide can alleviate some patients' headaches. This might suggest that pituitary adenomas sometimes secrete chemicals that activate the trigeminovascular system and that the administered somatostatin antagonists act both on the somatostatic receptor 2 (SST-2) acromegaly-related receptors and also on other receptors such as SST-5 which might be involved in headache regulation.[23]

Other secondary headaches

Secondary headaches were also a big focus at EHMTIC. An animal model of medication overuse headache (MOH) showed that mice who underwent daily injections of acetaminophen and aspirin for 30 days had increased anxiety-like behaviour and hyperexcitability in their amygdala compared to control mice (Poster refs 113, 253). In MOH, a multicentre study showed that expertise of the headache centre and low levels of feeling in control of the headache were predictors of dropout rates from a detoxification programme (Poster ref 390). It was also shown that detoxification without any intake of rescue medication is more efficient than detoxification with restricted intake (Poster ref 062). A human study on idiopathic intracranial hypertension (IIH) showed that truncal weight loss is associated with clinical resolution of IIH (Poster ref 062). Furthermore, glucagon like peptide-1 (GLP-1) reduces raised intracranial pressure in animals (Poster ref 406). Since GLP-1 therapy promotes weight loss this could be a future treatment of IIH. Post-traumatic headache (PTH), a major type of secondary headaches, currently lacks relevant preclinical models. Two models were presented at the conference describing PTH in mice and rats subjected to mild closed head injury (Poster ref 101). Increases in the sensory neuropeptides CGRP and PACAP were reported in the trigeminal nucleus caudalis as well as a persistent susceptibility to the common migraine trigger, nitroglycerin, both of which may be putative causes of PTH following mild traumatic brain injury. A clinical study showed that disability from PTH is compounded by post-traumatic stress disorder (Poster ref 106).

Headache in children

There are five 'episodic syndromes that may be associated with migraines': 1) infant colic (or more appropriately called 'paroxysmal fussing in infancy'; 2) benign paroxysmal torticollis; 3)

benign paroxysmal vertigo; 4) abdominal migraine; and 5) cyclic vomiting syndrome.[24,25] These syndromes are associated with a maternal history of migraines and an increased odds ratio of developing subsequent episodic syndromes and then migraines later in life.[26,27] The chronologic progression of these syndromes offers a window on the neurodevelopmental component of migraines.[24] The migraine prevalence in 10 year-old children is 5%, which makes migraine more prevalent than epilepsy.[24] In addition, paediatric migraines are associated with poorer academic performance, underlining the importance of proper treatment. Child migraine attacks are acutely managed with ibuprofen oral, rizatriptan 10 mg oral dissolving tablets, zolmitriptan 5 mg nasal spray, and sumatriptan 10 mg nasal spray.[28]

Trigeminal neuralgia: mechanisms lead to successful treatment

Ralf Baron gave an interesting talk detailing how the pain field has learned from the headache field in that precise phenotyping of patients into relevant disease categories can inform treatment guidelines. Neuropathic pain patients are a very heterogeneous population that perceive their pain quite differently. Therefore, sensory profiling of patients into relevant subgroups may help to determine an individualised mechanism and individualised treatment. Professor Baron's group performed quantitative sensory profiling on 1,000 neuropathic pain patients to determine their sensory profiles; 34% displayed thermal hyperalgesia, 29% displayed sensory loss and 37% displayed mechanical hyperalgesia. Such sensory profiling of patients is important as sodium channel blockers that were in development for neuropathic pain failed to show efficacy in phase III trials, however, a follow-on study stratifying patients into sensory profile subgroups revealed that oxcarbazepine (a sodium channel blocker) was efficacious for patients with thermal hyperalgesia but not for those with sensory loss.[29] Trigeminal neuralgia patients can be stratified based on whether they have background pain. Patients with background pain had decreased detection thresholds, while patients without persistent background pain had thermal and mechanical hyperalgesia with generalised subclinical hypoesthesia.[30]

The global burden of headache

In 2013, headache ranked third highest among all causes of disability.[31] However, currently, new population based studies are being conducted in countries not previously included in GBD 2013. In addition, the EUROLIGHT study has shown that headache is not only an ictal disease, but also influences patients between attacks. Lastly, big population studies have shown that migraine is undertreated and underdiagnosed.[32] Collectively, these findings could cause headache to rank even higher in the next GBD, which will further raise awareness of the huge, global burden of headache diseases.

Conclusion

The EHMTIC 2016 congress highlighted the current understanding of the pathophysiology of headache and migraines, emphasising the role of the brainstem and hypothalamus. Throughout the 4 days the role of sleep, sex hormones, circadian rhythm, the hypothalamus, and CGRP were all discussed. Promising results on 5-HT1F agonist lasmiditan and the antibodies targeting CGRP were presented, raising hope that these drugs will become available in the near future. Different headache phenotypes were also highlighted with

insights into the pathophysiology of cluster headaches, paediatric headaches, pituitary adenoma-related headaches and secondary headaches. A lot of progress has been made since the last EHMTIC in Denmark, and no doubt the upcoming IHS conference next year in Vancouver will bring further developments in what is an exciting time in the field of headache research.

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