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Inflammation and migraine

As part of the “Inflammation and migraine” session at the 19th Congress of the International Headache Society (IHC), Prof. JIHC Schoenen provided an overview of the clinical evidence for the role of inflammation in migraine. Following his presentation, Prof. Turgay Dalkara discussed the inflammasome story in relation to migraine.

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The non-migraine headache – a forgotten problem?

Our knowledge of the underlying mechanisms of migraine has improved in recent years, leading to the development of novel target-based approaches for its treatment. However, the non-migraine headache remains an under-researched area, despite being one of the main causes of disability worldwide.[1] At a special lecture during the 19th Congress of the International Headache Society (IHC), Prof. Rigmor Jensen discussed the importance of furthering our understanding of the non-migraine headache, focusing on tension-type headache, medication-overuse headache and cluster headache.

Tension-type headache (TTH)

Although TTH is highly prevalent in the general population, it is often not recognised or treated appropriately in specialised clinics. Prof. Jensen described how many of her patients consider TTH to be a normal phenomenon and not a serious disorder. However, in its frequent and chronic forms, TTH can have a significant impact on quality of life for patients.[1]

Prof. Jensen emphasized that although migraine and TTH have some overlapping features, they are separate disorders. Clinicians should be aware that they frequently coexist in patients and both diagnoses should be applied. In terms of TTH management, there are no specific therapies for TTH and its management often involves triptans. One study showed that patients with TTH had deteriorated neck and shoulder muscle function compared to healthy controls;[2] therefore, some patients may benefit from posture correction and normalization of muscle function. Prof. Jensen highlighted the need for further research into the underlying mechanisms of the disease in order to develop specific therapies to improve the management of TTH.

Medication-overuse headache (MOH)

Prof. Jensen stated that although MOH is estimated to affect approximately 63 million individuals worldwide, MOH is both a treatable and preventable condition. Discontinuation of the treatment causing MOH has been shown to increase patient productivity and decrease direct healthcare costs.[3] Complete withdrawal of the treatment causing MOH is considered both more effective and more feasible than restricting its intake to detoxify patients.[4,5]

Prof. Jensen highlighted that even short-term use of painkillers may be harmful and she urged clinicians not to overprescribe medication in the management of MOH. In her opinion, optimal care for MOH requires information and education for both patients and clinicians.

> “There is so much interest in headache disorder, and we have to go home and raise awareness in our countries.

Prof. Rigmor Jensen (University of Copenhagen, Denmark)

Cluster headache

Prof. Jensen began her discussion of cluster headaches with an overview of the temporal symptom development of a cluster headache attack. Prof. Jensen suggests that recognition of the symptoms in the pre-ictal phase (i.e. local painful and autonomic symptoms) could help inform early treatment strategies, before the pain phase occurs.[6]

Although the diagnostic delay for cluster headache has decreased over time,[7] it still remains a problem in cluster headache management. A Danish cohort study showed that the diagnostic delay for cluster headaches was approximately 6.2 years for both men and women, with misdiagnosis of cluster headache being more prevalent among women compared with men (61% vs 46%).[8]

Prof. Jensen concluded her lecture by emphasizing that non-headache disorders pose a significant public health problem. To improve the care of patients with non-migraine headaches, Prof. Jensen believes that the responsibility of raising disease awareness and providing education lies with the clinician.

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Inflammation and migraine

The mechanisms underlying chronic migraine are unresolved, but are hypothesized to involve a degree of inflammation.[1] At a session titled "Inflammation and migraine" during the 19th Congress of the International Headache Society (IHC), Prof. JIHC Schoenen (University of Liège, Belgium) provided an overview of the clinical evidence for the role of inflammation in migraine. Following Prof. Schoenen's presentation, Prof. Turgay Dalkara (Hacettepe University, Turkey) discussed the inflammasome story in relation to migraine.

Clinical evidence for the role of inflammation and anti-inflammatory drugs in migraine

Prof. Schoenen stated that molecular markers, imaging studies, sensitization of nociceptors, and the effect of non-steroidal anti-inflammatory drugs (NSAIDs) provide clinical evidence of neurogenic inflammation in migraine. Changes in the levels of inflammatory markers – including cytokines and cyclooxygenase-2 – have been shown during migraine attacks.[2,3] However, the relevance of these changes to migraine pathophysiology is unclear and requires further research.

Although imaging studies show no disruption to the blood–brain barrier during migraine attacks with or without aura,[4,5] results of a recent imaging study showed neuroinflammation in the visual cortex and nociceptive processing areas in migraine with aura.[6] In Prof. Schoenen's experience, NSAIDs are almost as effective as oral triptans for the treatment of mild/moderate migraine. However, this does not prove the role of inflammation in migraine, as NSAIDs can also have central effects.

Prof. Schoenen concluded his presentation by agreeing with a proposal by Prof. Lars Edvinsson and his colleagues in a recent review, which states that chronic migraine involves neurogenic neuroinflammation in the trigeminovascular system.[1]

The inflammasome story and migraine

Prof. Dalkara described a signaling pathway between stressed neurons and meningeal trigeminal afferents, which may explain how migraine headaches are generated.[7] According to Prof. Dalkara, a single cortical spreading depression (CSD) triggers a sequence of inflammatory signaling in the parenchyma. This leads to a sustained release of cytokines, prostanoids and nitric oxide from glia limitans that activates trigeminal nociceptors around glia vessels. This pathway may trigger headache when neurons are stressed.[7]

Prof. Dalkara explained that migraine triggers such as sleep deprivation can induce excitatory synaptic stress by reducing availability of glycogen-derived glucose and lowering the threshold for CSD induction.[8] Prof. Dalkara also highlighted in the conclusion of his presentation that prolonged activity in the locus coeruleus reduces the glycogen availability required during prolonged excitatory transmission.

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Patient's perspective: challenges with migraine prevention

In her presentation at a Teva-sponsored satellite symposium that took place during the 19th Congress of the International Headache Society (IHC), Audrey Craven (Migraine Association of Ireland) highlighted how important it is to consider the perspective of patients when treating migraine.

Challenges faced by patients with difficult-to-treat migraine

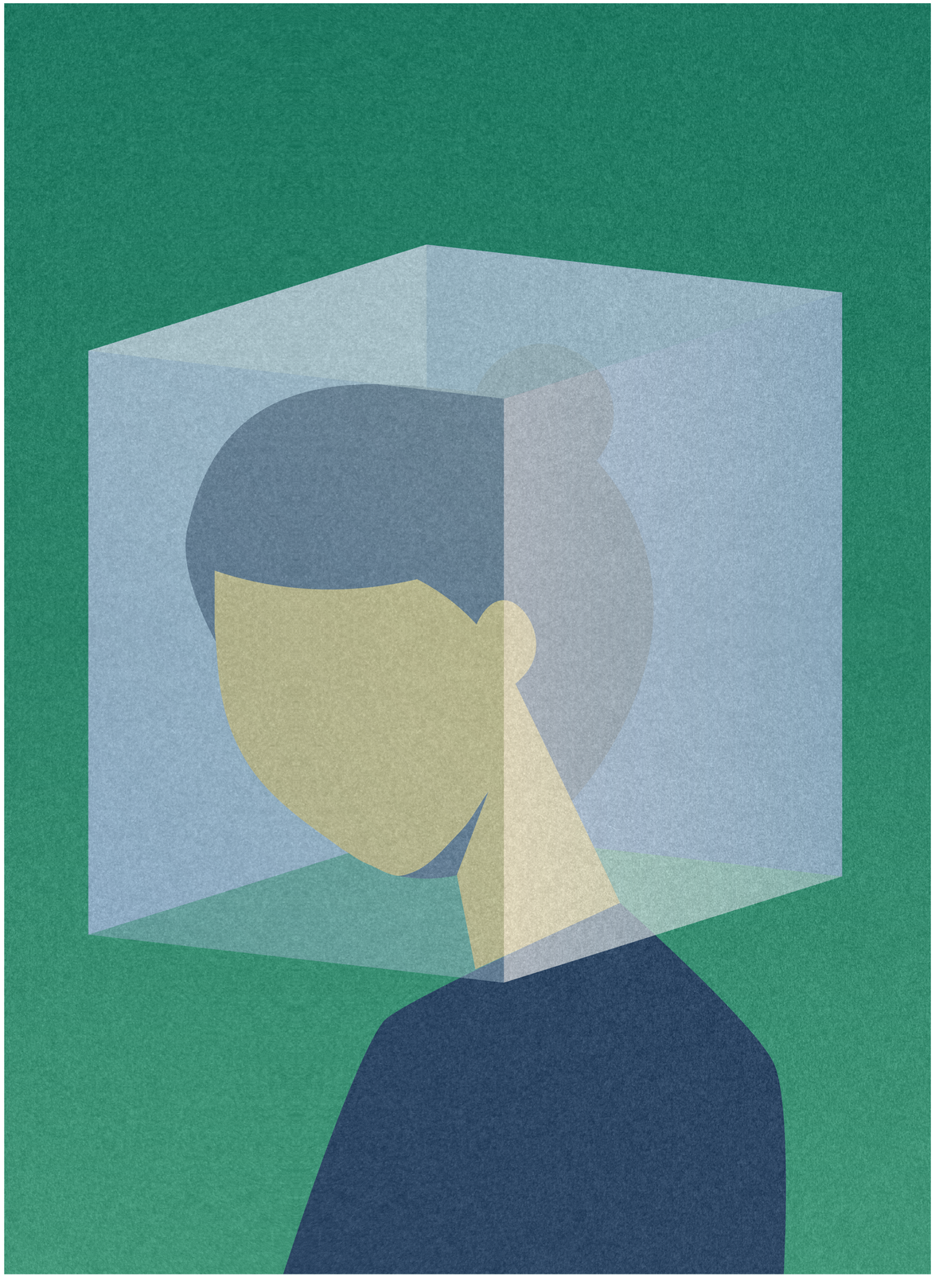
During her presentation, Audrey Craven highlighted challenges that, in her opinion, are faced by patients with difficult-to-treat migraine. One key challenge is the limited access of preventive treatments to patients who do not receive headache-specialized treatment. A recent longitudinal, web-based study has highlighted accessing medical consultation, being diagnosed accurately, and receiving appropriate pharmacological interventions as the three key barriers to good medical care.[1]

Ms Craven stated that migraine patients are misunderstood and stigmatized as a result of their migraine affliction. This is supported by a recent global, cross-sectional survey of patients in which 85% of all respondents reported negative aspects of living with migraine, including feeling helpless, depressed and misunderstood.[2]

Finishing her analysis of the challenges faced by patients, Ms Craven described how migraine is a very disabling disease that impacts patients, their relatives and society as a whole. In her opinion, the presence of comorbidities further amplifies the negative effect of migraine on quality of life.

The unmet needs of patients with migraine

CGRP is primarily located in C and Aϑ sensory fibres originating from the dorsal root and trigeminal ganglia, as well as the CNS.[2] Activation of the trigeminal system results in the release of CGRP, which in turn leads to vasodilation and release of nitric oxide, and



ultimately causes pain.[2] CGRP is widely distributed in the central and peripheral nervous systems, where increased levels are found in patients with migraine.[3] In addition to the therapeutic potential of CGRP, it could also serve as a diagnostic biomarker of migraine.

Stopping pain where it starts

To highlight unmet needs in the management of migraine, Ms Craven presented a series of anonymous quotes collected by email from individual patients with migraine, emphasizing their experience of living with the disease. She characterized how migraine can result in emotions of despair, anguish, hopelessness and isolation.

1. **Despair:** *"I'm not okay, I lost it all, sports, husband, friends, job, independence and will to live…"*

2. **Anguish:** *"I'm nobody now, not a little bit of the person I used to be and I hate this… so much now, I hate myself and I can't even look at this pale face with black bags and drooped eyes in the mirror."*

3. **Hopelessness:** *"I lost my dream job due to my migraine, no other to blame, same happened with athletics."*

4. **Isolation:** *"I used to win medals and now I'm a "something" who can barely walk… someone who has to wait for her boyfriend to have a shower."*

> Migraine not only affects the person who lives with the condition, but it also affects the family and society at large.

Audrey Craven (Migraine Association of Ireland)

Hope for patients with difficult-to-treat migraine

To conclude her talk, Ms Craven described her hope that the feelings of despair, anguish, hopelessness and isolation experienced by patients will be improved as the standard of care for migraine improves. Specifically, she believes that despite the many challenges faced by patients with difficult-to-treat migraine, there is still hope for such patients and those who experience comorbidities.

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What is the reason behind the higher prevalence of migraine in females than in males?

> Just having estrogen around – in males or females – is associated with a higher prevalence of migraine.

Prof. Anne MacGregor (Barts Health NHS Trust, United Kingdom)

The lifetime prevalence of migraine is much higher in females than in males.[1] During a One Topic, Two Views session at the 19th Congress of the International Headache Society (IHC), Prof. Anne MacGregor (Barts Health NHS Trust, United Kingdom) and Prof. Dale Nyholt (Queensland University of Technology, Australia) discussed whether hormonal fluctuations or genetics are the key factor for this difference in prevalence between females and males.

Are hormonal fluctuations the key factor behind the higher prevalence of migraine in females versus males?

Adolescence and perimenopause are periods of increased migraine prevalence in females.[1] Prof. MacGregor described how migraine is affected by fluctuating estrogen levels, with clinical evidence to support estrogen 'withdrawal' as a trigger of attacks of menstrual migraine without aura, while high estrogen levels can trigger migraine with aura. One study showed that preceding ovulation, estrogen levels were relative to normal in migraine patients with aura, but were increased in migraine patients without aura.[2] These results suggest that estrogen is an important factor in the clinical expression of migraine.

Prof. MacGregor also highlighted that estrogen is not just an ovarian hormone, but is also active in the pathophysiology of migraine in the brain. She stated that estrogen affects the trigeminovascular system, nitric oxide production, serotonergic actions, and also calcitonin gene-related peptide (CGRP) expression and function.

Prof. MacGregor emphasized that increased levels of estrogen is also associated with migraine prevalence in males. This is supported by a study in non-obese males with migraine who showed increased levels of estrogen and evidence of androgen deficiency compared with healthy volunteers.[3] She concluded by highlighting the importance of not only hormonal fluctuations, but also increased levels of estrogen in the prevalence of migraine.

Are genetic differences between males and females the main factor responsible for the higher numbers of migraine in females versus males?

Prof. Nyholt opened his presentation by describing how the heritability of migraine indicates that genetic factors are important. He discussed the results of twin studies in migraine, which found no conclusive evidence for genetic sex-specific effects and no significant sex differences in the magnitude of genetic influences.[4]

Prof. Nyholt then described the findings of molecular genetic studies, focusing on genome-wide association studies (GWAS) of single-nucleotide polymorphisms (SNPs) in migraine cases. Prof. Nyholt described how an analysis of 146 index SNPs with association with migraine found that the effect sizes were similar in male and female subgroups. However, as the SNPs were identified via a fixed-effect meta-analysis, these results were not surprising.[5] His own research showed that no female sex hormone genes have been robustly implicated in migraine GWAS. Prof. Nyholt stated that any differences in common genetic risk across females and males is far outweighed by the similarities.

He concluded that the difference in migraine prevalence between the sexes is most likely due to critical hormone-responsive genes, shared by both males and females, being influenced differently in the alternative hormonal environment of the male or female throughout their lifespan.

The session closed with a consensus that both hormones and genetics play a significant role in the difference in migraine prevalence between males and females. The interplay between these factors is complex, with many questions yet to be answered.

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Is the migraine cortex inherently hyper-responsive: re-examining the defected habituation system

During a debate session at the 19th Congress of the International Headache Society (IHC), Prof. Gianluca Coppola (Sapienza University of Rome) and Prof. Trond Sand (Norwegian University of Science and Technology) presented evidence supporting their opinions on the question "Is the migraine cortex inherently hyper-responsive?"

Prof. Gianluca Coppola: The migraine cortex is inherently hyper-responsive

Prof. Coppola began his presentation by describing the dual process theory, which includes two distinct and independent processes which govern the behavioral response to repetitive sensory stimulation.[1] The first process is sensitization, which occurs at the beginning of a test session and is responsible for the transitory increase in response amplitude.[2] The second process is habituation, which occurs throughout a test session and is responsible for a delayed response increment.[2]

Prof. Coppola proceeded to highlight evidence supporting the hypothesis that potentiation, rather than habituation, characterizes visual evoked potentials in migraine patients between attacks.[3] In one key study designed to evaluate this hypothesis, electroencephalography (EEG) was used to compare the neural response to electrical stimulation of the median nerve in healthy volunteers and patients with migraine during the interictal phase.[4] Whereas a habituation of responding was observed in healthy volunteers, a potentiation of visual evoked potentials was observed in patients with migraine with and without aura.
To conclude his presentation, Prof. Coppola stated his opinion that this body of evidence is sufficient to demonstrate that the migraine cortex is inherently hyper-responsive.

> “In the presence of a recurrence of attacks, central sensitization amplifies and persists chronic migraine.
>
> Prof. Gianluca Coppola (Sapienza University of Rome)

Prof. Trond Sand: The migraine brain is not inherently hyper-responsive

Prof. Sand stated that although the results presented by Prof. Coppola are promising, there is a need for demonstrating the reproducibility and reliability of the effects observed during these studies. Specifically, Prof. Sand highlighted the importance of ensuring analysis of data from studies is appropriately blinded. According to Prof. Sand, studies that use blinded recording and analysis of data have not found a lack of habituation in migraine patients compared with healthy controls. In one study, visual evoked potentials in 41 interictal migraineurs and 30 controls were compared, with habituation observed in both groups.[5]
Were the hyper-responsivity hypothesis to be correct, potentiation should have been observed among patients with migraine.
To conclude his presentation, Prof. Sand reaffirmed the importance of blind recording and analysis as a method of controlling for unconscious bias. Furthermore, he highlighted the importance

> “It is very important to focus on technical recording standards in neurophysiology.
>
> Prof. Trond Sand (Norwegian University of Science and Technology)

of reducing positive and negative bias in research. In positive bias, unexpected findings are actively discarded as being wrong. In negative bias, unexpected outliers may be removed, increasing the likelihood of achieving a hypothesized result.

Conclusion: An exciting time for migraine research

Following their presentations, both Prof. Coppola and Prof. Sand highlighted that new technologies and methods of data analysis have increased the speed at which migraine is being understood. However, this research needs to be rigorous, with replication of important results.

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Non-invasive neuromodulators' role in the treatment of migraine and cluster headache: do they work and how?

Non-invasive neuromodulation alters neural activity through the stimulation of nerves and neural tissue.[1] Neuromodulation therapies may provide an alternative treatment option to drug therapies for the treatment of migraine and cluster headache. During the 19th Congress of the International Headache Society (IHC 2019), Dr Simon Akerman (University of Maryland, USA), Dr Anna Andreou (Guy's and St Thomas' NHS Trust, United Kingdom) and Prof. David Yarnitsky (Rambam Medical Centre, Israel) discussed the role of non-invasive neuromodulation devices for the treatment of migraine and cluster headaches.

Dr Simon Akerman: Non-invasive vagus nerve stimulation (nVNS)

Dr Akerman began his presentation by describing clinical trial data evaluating the efficacy of nVNS for the treatment of migraine and cluster headache. In migraine, results of a randomized, sham-controlled trial are suggestive of effective pain relief and tolerability for the acute treatment of episodic migraine.[2] In cluster headaches, pooled data from two randomized, sham-controlled trials showed that nVNS was effective in acute treatment for episodic cluster headache.[3] It was noted that the efficacy of nVNS is yet to be determined for the preventive treatment of chronic migraine and cluster headache.

Dr Akerman discussed the mechanisms of action of nVNS, highlighting results of a preclinical migraine model that suggests nVNS engages dural-trigeminovascular mechanisms.[4] Dr Akerman also described how nVNS engages cortical neurons, demonstrated by effects of cortical spreading depression (CSD). Dr Akerman concluded that via both direct and indirect effects, nVNS engages and modulates migraine and cluster headache-related descending trigeminal and ascending cortical responses.

Dr Anna Andreou: Single-pulse transcranial magnetic stimulation (sTMS)

As part of her presentation, Dr Andreou presented efficacy data for the treatment of migraine with sTMS. A randomized, sham-controlled trial in acute migraine with aura showed increased freedom from pain with sTMS compared with sham stimulation.[5] In terms of preventive treatment for migraine, results of an open-label, observational study showed a significant mean reduction of headache days from baseline compared with a statistically-derived placebo estimate.[6]

Using data from animal models of migraine, Dr Andreou described how the mechanisms of action for sTMS affect both cortical and thalamic activity. In animal models of migraine with aura, sTMS was shown to block CSD frequency and increase the CSD threshold.[7] Single neuron extracellular electrophysiology has shown that sTMS also modulates trigeminovascular neuronal activity within the thalamus[7] and alters dopaminergic hypothalamic signaling.

> “In the future, we may have a magnet in our phone to treat our headaches.
>
> Dr Anna Andreou (Guy’s and St Thomas’ NHS Trust, United Kingdom)

Prof. David Yarnitsky: Non-cranial nerve stimulation

Prof. Yarnitsky discussed how patients with migraine are unable to suppress pain in the same way as people without migraine. This is supported by study findings that suggest patients with migraine have deficient conditioned pain modulation (CPM) compared with healthy controls.[8,9] Prof. Yarnitsky described CPM an endogenous analgesia mechanism, in which conditioning stimulation inhibits pain in remote body regions.

Prof. Yarnitsky proceeded to describe remote electrical neuromodulation (REN), a novel acute migraine treatment in which upper arm peripheral nerves are stimulated to induce CPM. In a recent randomized, sham-controlled study, REN was shown to be more effective than sham stimulation in the treatment of episodic migraine pain.[10] Prof. Yarnitsky concluded his presentation by emphasizing that although REN seems to be an effective and well-tolerated non-pharmacologic treatment for episodic migraine, the proposed mode of action for REN via CPM activation still needs to be proven through experimental research.

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