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### Editorial board:

Messoud Ashina  
Stefan Evers  
Oliver Summ  
Carol Taylor



## Letter from the President

Messoud Ashina

Dear Colleagues,

Much progress has been made since our last meeting at the 19th Congress of the International Headache Society (IHC) in Dublin, Ireland in September 2019.

Please click to read this report in [Portuguese](#), [Spanish](#) or [Mandarin](#).

### Electronic Media

The IHS is more active than ever before on social media platforms. We are now regularly providing new content to engage with our key audiences. To further increase visibility, we expect to launch a new website this summer. This is meant to increase website traffic and create a brand identity that meets the demands of a technological age.

### Education

The IHS has now initiated an important project aimed to create a high-quality online educational platform. Webinars will soon be hosted by IHS to better communicate educational content to hundreds of participants worldwide in real-time. This will hopefully also incentivise more healthcare professionals to join IHS.

### Strategic Meeting in Copenhagen

A strategic IHS meeting was recently held in Copenhagen, with many great discussions on how to build an even more prosperous future for IHS. The collaborative spirit was very inspiring and made it clear that the wheel of progress is placed on our collective shoulders. Together, we will cast our eyes towards tomorrow and go as far as our collaborative efforts take us.

**Messoud Ashina**  
[ashina@dadlnet.dk](mailto:ashina@dadlnet.dk)



## Update from the Honorary Secretary

Stefan Evers

I am pleased to give an update on IHS activities since the last Newsletter distributed in November 2019.



Israeli Headache  
Society joins IHS as  
an Affiliate Member  
Society bringing the  
number to 53

Apply now for the IHS  
Fellowship 2020

## Membership

After a very successful year for membership numbers in 2019, IHS continues to welcome new members, and so far in 2020 member renewals have been excellent. If you are not a member and would like to join, or if you have not yet renewed, please visit the [IHS website](#).

In December 2019 IHS welcomed the Israeli Headache Society as an Affiliate Member Society, bringing the number of IHS national member societies to 53.

## 2020 IHS Fellowship

Application for the 2020 IHS fellowship award is now open. The award aims to support innovative and impactful research from young investigators, promote the career of young investigators in the field of headache, and increase the knowledge base of headache disorders. Applications for basic or clinical science headache research, or a combination of basic and clinical research, will be considered. We particularly encourage young clinical researchers to submit an application.

The deadline for applications is 1 July 2020 and the value is £ 50,000 for a 1-year fellowship. For more information and an application form please visit the [IHS website](#).

## ICOP 2019

Arne May, Editor-in-Chief of Cephalalgia, has worked closely with a collaborative group consisting of members of the Orofacial and Head Pain Special Interest Group (OFHP SIG) of the International Association for the Study of Pain (IASP), the International Network for Orofacial Pain and Related Disorders Methodology (INFORM), and the American Academy of Orofacial Pain (AAOP) to develop the International Classification of Orofacial Pain (ICOP). This was published in Cephalalgia in February 2020 and the Editorial is available in this Newsletter.

IHS welcomes interested parties to translate the ICOP – please [contact IHS](#) for more information.

## Guidelines

The Clinical Trials Guidelines Committee has been working on updating the 'Guidelines for Controlled Trials of Preventive Treatment of Migraine Attacks in Episodic Migraine in Adults'. The document is now undergoing review by IHS members and will be published later in 2020.

During 2020 IHS will also develop guidelines on neuromodulation in migraine, idiopathic intracranial hypertension, cluster headache, registries on real life data and recommendations for health technology assessment (HTA) for the treatment of headache disorders.

## IHS research grants

For the first time in 2019 the IHS Board opened applications for research grants for scientific projects. Congratulations are offered to the two projects which were selected from over 30 applications received, each receiving € 75,000:

- Menstrual migraine: estrogen influences migraine susceptibility by affecting the balance of oxytocin and CGRP signaling. Principle investigator: Kristian A Haanes. Co-investigators: Lars Edvinsson (Lund, Sweden), Diana Krause (Irvine, USA). Research location: Glostrup Research Park, Copenhagen University Hospital, Copenhagen, Denmark
- BIOMIGRAINE: A multidisciplinary approach to the identification of BIOMarkers of MIGRAINE: a proof of concept study based on the stratification of responders to CGRP monoclonal antibodies. Principle investigator: Patricia Pozo Rosich. Co-investigators: Marta Torres-Ferrus (Barcelona, Spain), Cristina Tassorelli and Roberto de Icco (Pavia, Italy), Arne May and Christian Ziegeler (Hamburg, Germany). Research location: Headache Clinical Unit & Research Group, Vall d'Hebron Institute of Research, Barcelona, Spain

## International Classification on Facial Pain published in Cephalalgia

## Overview of publications which contribute greatly to the understanding and treatment of headache disorders

### Looking to the future

The Board of Trustees and representatives of some committees held a strategic meeting in Copenhagen at the end of February to discuss future activities and necessary administrative changes in IHS. Although it is still too early to publish any details, we would like to inform our members that IHS as a growing scientific society will have more impact and more activities in the future which need a more professional management and participation of our members. We also will have growing activities in social media and public relations for which we will depend on the support of all our members. More information will be shared in the coming months.

### IHS Social Media

For all the latest IHS and headache news, don't forget to follow IHS on our social media channels.



Stefan Evers  
[everss@uni-muenster.de](mailto:everss@uni-muenster.de)

## Cephalalgia highlights 2019 – Junior Editors' Choice



Kuan-Po Peng,  
Shih-Pin Chen,  
Larus  
Gudmundsson

In research on headache disorders in 2019, migraine remained the focus of attention as the antibodies against calcitonin gene-related peptide (CGRP) and its receptors have become available in several countries along with the publication of phase III clinical trials of the newer generation oral CGRP receptor antagonists.<sup>1,2</sup> Aside from the overshadowing CGRP research, several other interesting studies have been published. We provide an overview of the publications that, in our opinion, contribute greatly to the understanding and treatment of headache disorders. Of note, the selection for the list is subjective and does not include all research works published in 2019 worthy of mention. We hope that our selection serves as a short summary and a catalyst to increase the interests of headache researchers. In the current editorial, we will discuss preclinical and clinical studies, which provide a better understanding of the disease mechanisms or a potential to future treatment targets.

### Preclinical studies

#### Cortical spreading depression and CGRP, limited convergence

Schain et al. examined how CGRP antibodies modulate cortical spreading depression (CSD) in a rat model. The authors found that CSD-induced vascular changes of pial arteries (brief dilatation followed by prolonged constriction), prolonged dilatation of dural arteries, and plasma protein extravasation (PPE) were unaffected by the administration of fremanezumab, an anti-CGRP antibody. Additionally, CGRP infusion did not induce dilatation in pial vessels but only dural vessels, which could be effectively blocked by fremanezumab.<sup>3</sup> Unlike the CSD scenario whereby dilatation of dural arteries was correlated with the occurrence of PPE, the CGRP-induced dilatation of dural arteries was not associated with PPE. Hence, although

Nav1.9 channel inhibitors might be a new treatment target for patients with MOH

PTH might be mediated through a CGRP-dependent mechanism and serves as the first step to PTH-specific treatment options

Newer targets other than CGRP remain to be explored for severely disabled chronic CH patients

fremanezumab could block CSD-evoked activation of A $\delta$  meningeal nociceptors and high-threshold trigeminovascular neurons,<sup>4</sup> the action of CGRP blockade is likely irrelevant to the CSD-evoked vascular or neurogenic inflammatory responses. Therefore, it is unlikely that a single model system could explain the pathophysiology of migraine, a disease considered biologically heterogeneous.

#### **New treatment target for medication overuse headache**

Bonnet et al. examined nitric oxide (NO)-induced activation of trigeminal neurons in an animal model of medication overuse headache (MOH) induced by a triptan. They found an abnormal activation of Nav1.9 channels in meningeal nerve fibres and dural afferent neurons in MOH mice, which subsequently triggers CGRP release, arterial dilation, and mast cell degranulation. The deletion of the *Scn11a* gene, which encodes the voltage-gated sodium channel Nav1.9, abrogates the NO-induced hypersensitivity.<sup>5</sup> Meanwhile, another clinical study showed that botulinum toxin A in combination with acute withdrawal provides no additional benefit over acute withdrawal alone.<sup>6</sup> Therefore, Nav1.9 channel inhibitors might be a new treatment target for patients with MOH.

#### **Animal model for post-traumatic headache has arrived**

The awareness of post-traumatic headache (PTH) has accumulated over the years; however, the underlying mechanisms remain poorly understood. Bree and Levy used a weight-drop device to induce concussion in rats. After the acute phase (by 2 weeks postinjury) of pain hypersensitivity had resolved, the authors could reproduce cephalic pain hypersensitivity by low-dose glyceryl trinitrate (GTN) administration in PTH mice but not in sham animals. This hypersensitivity can be inhibited by the treatment of either sumatriptan or anti-CGRP antibody.<sup>7</sup> This study suggests that PTH might be mediated through a CGRP-dependent mechanism and serves as the first step to PTH-specific treatment options.

#### **Clinical studies and advances in treatment**

##### **Role of CGRP in migraine and other headaches: the story continues**

The results of two phase III trials of CGRP antagonists (gepants) in the acute treatment of migraine, ubrogepant and rimegepant, have been published. In both randomised controlled trials, gepants were superior to placebo: 2-hour pain freedom 19.6% with rimegepant,<sup>1</sup> and 19.2–21.2% with ubrogepant;<sup>2</sup> however, the therapeutic gain (placebo-subtracted value) was low, only 7.6% with rimegepant,<sup>1</sup> and 7.4–9.4% with ubrogepant,<sup>2</sup> compared with other migraine-specific acute treatment options: 26% with sumatriptan<sup>8</sup> and 12.9–16.9% with lasmiditan (5-HT<sub>1F</sub> agonist).<sup>9</sup> Nevertheless, no head-to-head comparison has been conducted. It remains a question whether the effects of both gepants are clinically relevant. Besides, patients either with contraindications for or not responding to triptans were not investigated in gepant studies, and these are the patients who could specifically benefit from them.

##### **CGRP antibodies in treating cluster headache**

Two anti-CGRP antibodies have been studied on patients with cluster headache (CH). The study which evaluated the efficacy of fremanezumab for the prevention of episodic CH (NCT02945046) has been terminated early due to the results from a prespecified futility analysis.<sup>10</sup> Conversely, galcanezumab has been shown to be superior to placebo in reducing headache attacks in patients with episodic CH.<sup>11</sup> During weeks 1–3, the patients who received galcanezumab had a mean weekly reduction of 8.7 attacks with a therapeutic gain of 3.5 attacks. At week 3, 71% in the galcanezumab group versus 53% in the placebo group reached at least a 50% reduction in headache frequency.<sup>11</sup> Instead, the placebo-controlled study of galcanezumab in patients with chronic CH did not achieve the primary or secondary endpoints.<sup>12</sup> Newer targets other than CGRP remain to be explored for the severely disabled chronic CH patients.

## Response to medication in headache disorders may be genetically determined

## Important role of $K_{ATP}$ in migraine pathophysiology and blocking of the $K_{ATP}$ channel may be a potential target in migraine treatment

### Neuromodulation on patients with chronic CH

In a randomized, sham-controlled, parallel-group, double-blinded study, patients who received sphenopalatine ganglion (SPG) stimulation were more likely to achieve the primary endpoint, defined as relief from pain within 15 minutes (62.5% vs 38.9%,  $p = 0.008$ ).<sup>13</sup> Among the 45 patients in the SPG stimulation group, nine developed serious adverse events, four of which were implantation related. The SPG stimulation seems efficacious and well tolerated for patients with chronic CH.<sup>13</sup> Unfortunately, the producer of the device has filed for bankruptcy and whether the device will be available again remains unknown.

### Has the era of personalised medicine in headache disorders finally arrived?

It remains difficult to predict whether a patient responds to a specific medication, for example, an abortive medication like a triptan or a preventive medication like topiramate. Kogelman et al. interviewed 2,219 unrelated migraine patients, assessed their acute and prophylactic drugs response, and genotyped all of them and calculated their polygenic risk scores (PRS) for the likelihood of migraine.<sup>14</sup> Among all the medications investigated, the authors found an association between higher PRS, suggestive of a higher risk of migraine, and a positive treatment response to triptan (odds ratio [OR] 1.25, 95% confidence interval [CI] 1.05–1.49) but not other medications. They replicated their findings in an independent cohort comprising 5,616 triptan users with an OR of 3.20 (95% CI 1.26–8.14).<sup>14</sup> This is the first study to show that the response to medication in headache disorders may be genetically determined and the mechanism of how triptans work is closely related to the mechanism behind a migraine generation.

### Central or peripheral origin: the debate is everlasting

It has been long debated whether the origin of a migraine attack is central or peripheral. More to the debate, whether certain migraine-specific medications act peripherally or centrally. Sumatriptan has long been considered to act peripherally because of its hydrophilicity and theoretically poor CNS penetration. Deen et al. studied eight patients with a positron emission tomographic scan after the injection of a specific 5-HT<sub>1B</sub> receptor radiotracer. They found that after sumatriptan administration, the central 5-HT<sub>1B</sub> receptor binding in pain-modulating regions was reduced by 16%, suggestive of a binding of sumatriptan to central 5-HT<sub>1B</sub> receptors.<sup>15</sup> The mechanism by which it crosses the blood–brain barrier (BBB) is unknown. The finding in this study raises another interesting question: whether the newer generation migraine-specific medications, for example, anti-CGRP or CGRP receptor antibodies, could possibly cross the BBB and exert a central action? The theoretical probability of that is considered negligible given an intact BBB; however, some suggested that the BBB might be 'leaky' in certain variants of migraine with aura.<sup>16,17</sup> One recent animal study observed a small proportion (0.34%) of anti-CGRP antibodies in central regions like the hypothalamus, where an effective BBB is lacking.<sup>18</sup> Future studies are still needed to address whether a central effect of CGRP antibodies is possible.

### Potential new treatment target in migraine

ATP-sensitive potassium channels ( $K_{ATP}$ ) locate downstream in the signaling pathway of either CGRP or NO in triggering migraine. Al-Karagholi et al. investigated whether the opening of  $K_{ATP}$  is associated with a migraine attack. In a randomised, double-blind, placebo-controlled, crossover design, among the 16 migraine patients who received the infusion of levcromakalim, a  $K_{ATP}$  channel opener, 16 of 16 (100%) developed migraine attacks after levcromakalim compared to one of 16 (6%) after placebo.<sup>19</sup> This 100% induction rate is higher than other substances, such as GTN, CGRP, or sildenafil,<sup>19</sup> and therefore, a validation study is warranted. Nevertheless, the study suggests an important role of  $K_{ATP}$  in migraine pathophysiology and the blocking of the  $K_{ATP}$  channel may be a potential target in migraine treatment.

### Closing remarks

The articles selected reflect the tremendous contribution from different research groups to improve the treatment of headache disorders and to advance our understanding of their



disease pathophysiology. Aside from the CGRP antibodies and antagonists, new potential treatment targets have emerged thanks to the progress made in studies focusing on disease mechanism. Less progress has been made in fields concerning less frequent but disabling headache disorders, for example, chronic CH and facial pain disorders. In summary, it has been a good and fruitful year for headache research, and we look forward to an even brighter future in 2020.

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**International  
Classification of  
Orofacial Pain – a  
collaboration between  
IHS, IASP, INfORM and  
AAOP**

**We need to have cross-  
profession scientific  
and clinical agreement  
to study these diseases**

## Facial Pain is coming home – ICOP Editorial



Arne May

Chronic facial pain that has no dental cause is probably underdiagnosed but also certainly undertreated.<sup>1</sup> Because chronic facial pain is in most cases perceived orally or in the mandibular/maxillary region, patients consult dentists who do not find any dental pathology. When cranio-mandibular disorders have also been excluded it becomes clear that the patient needs to be seen by a pain specialist, but more often than not consults another dentist.<sup>2</sup> One of the reasons why we do not recognise chronic facial pain is that we know so little about it and have no specific treatments to offer. The consequence is a life-long odyssey for affected patients which often ends with all teeth removed and the pain still ongoing.<sup>3,4</sup> This situation resembles in many facets the situation of headache patients some 30 years ago.<sup>5</sup> The cornerstone allowing to study the pathogenesis and find highly specific treatments for headache has been the IHS International Classification of Headache Disorders (ICHD).<sup>6</sup> ICHD has proven to be extremely valuable and indeed indispensable for scientific and clinical progress in the field of headache medicine.

There are certainly several reasons for the fact that, compared to the headache field, the investigation and treatment options of facial pain disorders remained slow. An important factor was certainly the lack of a comprehensive facial pain classification.<sup>7</sup> By acknowledging and using such a classification we make sure that scientific progress is comparable between labs and that clinicians all over the world speak about the same disease when discussing for example atypical odontalgia. With the recent implementation of the first International Classification of Orofacial Pain (ICOP)<sup>8</sup> a huge step has been undertaken allowing standardised communication between professions, scientists and clinicians.

One of the enigmas of non-dental facial pain is the question whether facial pain is indeed a pain disorder in its own right or rather just a headache syndrome which slipped from the ophthalmic to the second and third trigeminal branch.<sup>5</sup> Headache is often referred to orofacial regions and may even be located exclusively within the orofacial region.<sup>9-11</sup> Orofacial pains that are referred to the head present a difficult clinical entity with manifold phenotypes. Rafael Benoliel was one of the first voices in the wilderness, never tiring to point out to headache specialists that the headache field needs to become interested in chronic facial pain.<sup>12</sup> And indeed facial pain and its many facets is not reduced to trigeminal neuralgia, we need to see facial pain as an independent and distinct trigeminal disorder and such syndromes need to find a home in the headache field. In order to investigate we need to distinguish<sup>13</sup> – the issue becomes important or indeed decisive when facial pain has to be distinguished from headache syndromes.<sup>9</sup> Facial pain has also been defined in the ICHD, but the facial pain chapter in ICHD excluded many dental and other facial disorders and thus was incomplete. With the advent of ICOP this has changed. The classification committee covered dentists, temporomandibular joint dysfunction (TMD) specialists, neurologists and psychologists and also included members of the Orofacial and Head Pain Special Interest Group (OFHP SIG) of the International Association for the Study of Pain (IASP), the International Network for

**New developments  
in pathophysiology  
and treatment are  
our long-term target  
and we need to use  
ICOP in scientific  
and daily life**

Orofacial Pain and Related Disorders Methodology (INfORM), the American Academy of Orofacial Pain (AAOP) and IHS. This represents the major associations involved in orofacial and head pain, raising the acceptance and strengthening the future of ICOP. For the same reason a lot of work went into harmonising ICHD and ICOP. The recent definitions of trigeminal neuralgia and TMD were copied 1:1 to avoid having different definitions for the same disease. As such ICHD-3 and ICOP can be cited *pari passu*, but given that ICOP is more specific for facial pain it should be favoured at the moment.

Classifications are definitions and definitions are per se agreements<sup>13,14</sup> and the (in the pain field) unparalleled success story of headache has taught us that we need to have that agreement in order to study these diseases.<sup>9</sup> Starting with a unifying and internationally accepted classification such as ICOP<sup>8</sup> we start turning around and redefining the field of facial pain and also strongly encourage active collaboration.<sup>15</sup> New developments in pathophysiology and treatment are our long-term target and we need to use ICOP in scientific and clinical daily life – starting today.

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## Cluster Headache Awareness Day

March 21st

#ClusterHeadacheDay2020

#ClusterDay20



International  
Headache Society

Visit the IHS Twitter account to see presentations from  
key opinion leaders for Cluster Headache Awareness Day



We explored the retinal-thalamocortical pathways that may be responsible for abnormal processing of thalamic visual inputs commonly observed in migraine patients

## IHS 2018 Fellowship reports



Olivier Brock, Belgium

### The role of the visual thalamus in migraine

**Fellowship from August 2018 to August 2019**  
**King's College London, London, UK**  
**Mentor: Phillip R Holland**

The main aim of our project was to explore retinal-thalamocortical pathways that may be responsible for abnormal processing of thalamic visual inputs, commonly observed in migraine patients. We predicted that thalamocortical dysregulation may lead to altered cortical excitability and modified susceptibility to migraine aura. Lately, a refined transgenic Cre reporter mouse model based on the expression of the *Sox14* transcription factor has been validated as a specific tool to modulate the activity of GABAergic interneurons located in the dorsal (d) part of the lateral geniculate nucleus (LGN). Using this specific mouse model, we precisely modulated the activity of GABAergic interneurons located in the dLGN by using the latest state-of-the-art techniques such as chemogenetics (DREADDS) and viral-based cell ablation. We then determined its impact on clinically relevant migraine-related phenotypes in mice such as cortical spreading depression (CSD; aura), facial mechanical hypersensitivity (cephalic allodynia) and aversion to light (photophobia).

We validated the DREADDS approach by showing an increase of dLGN interneuron activation following stereotaxic targeting of dLGN interneurons with an excitatory DREADDS virus and administration of the DREADDS specific ligand CNO in *Sox14<sup>Cre/+</sup>* mice. We then established



MTIS 2018, London

five cohorts of mice (WT, *Sox14<sup>Cre/+</sup>* and dummy virus, *Sox14<sup>Cre/+</sup>* and excitatory DREADDS, *Sox14<sup>Cre/+</sup>* and inhibitory DREADDS, *Sox14<sup>Cre/+</sup>* and dTA virus (ablation); all injections targeted dLGN only). We initially demonstrated that CNO alone or a dummy virus lacking the excitatory receptor component had no impact on CSD thresholds. In comparison, the active excitatory DREADD construct that facilitated activation of visual feedforward GABAergic interneurons in the dLGN decreased the number of KCL-induced CSDs over 1 hour; however, their inhibition or ablation had no impact. This confirmed our primary hypothesis that local thalamic inhibition may be a novel target for decreasing thalamocortical excitability with important implications

The IHS fellowship allowed a smooth transition into the headache field by integrating into one of the most prestigious research labs



Electrophysiology Lab, London

research labs conducted by Philip Holland. He has been a very understanding and helpful mentor allowing me to bring and develop my own ideas. I acquired many new skills and techniques which now make me feel comfortable within the headache field. I attended two congresses (MTIS 2018 and IHC 2019) where I got the opportunity to present my results and foster some future collaborations. Overall, it has been a fantastic year and I am now applying for larger fellowships to continue my progress towards establishing my own research group exploring sex differences in primary headache disorders, and establishing myself as a principal investigator in the migraine field. The IHS fellowship represents a strong and meaningful support for such applications.

for migraine aura susceptibility and attack triggering.

In two final experiments, mice were primed with nitroglycerin (clinical migraine trigger) and assessed for light aversion or facial mechanical hypersensitivity following a bright light stress paradigm. Nitroglycerin-induced sensitisation was not affected by GABAergic interneuron activity modulation/ablation.

The IHS fellowship allowed a smooth transition into the headache field by integrating into one of the most prestigious



Headache Group, King's College London



Anisa Dehghani, Iran

## Parenchymal neuroinflammation and pain behaviour upon optogenetically-induced cortical spreading depolarisation in mice

Fellowship from February 2019 to February 2020

Leiden University Medical Centre, Department of Human Genetics, Migraine Group, Leiden, Netherlands

Mentor: Arn van den Maagdenberg

I focused on inducing cortical spreading depression (CSD) in a non-invasive manner with optogenetics to find the threshold for the induction of neuroinflammation and pain mimics in relation to the number of CSDs, without confounding factors of recent invasive surgery or the use of a restrainer. To further increase the translational value of the work we extended the research to mouse mutants that carry the S218L missense mutation in the  $\alpha_1$  subunit of



voltage-gated  $\text{Ca}_{v2.1}$  channels that have been linked to FHM1, and can be considered a valuable mouse model to study certain aspects of migraine. Importantly, the mutant mice allowed me to investigate neuroinflammation and pain behaviour in the context of a hyperexcitable brain with an increased susceptibility to CSD. I assessed the consequences of optogenetically-induced CSD on the extent of neuroinflammation in the context of HMGB1 release at different timing points, and

simultaneously, the occurrence of pain-related behaviours, separately for female and male mice. To further enhance the clinical relevance of the study, I tested the effect of TAT-Panx-308, which is an interfering peptide that mimics the C-terminal epitope of Panx1 including the Y308 site and blocks activation of Panx1 channels, as a potential novel drug for the treatment of migraine.

CSDs were non-invasively induced by optogenetics in freely moving mice. The neuroinflammatory marker HMGB1 in (sub)cortical brain areas, and the neuronal activation marker pERK in trigeminal ganglia (TG) were studied by immunohistochemistry in WT and FHM1 mice with and without CSDs. Pain-related behaviours were analysed in all conditions. Effects of the Panx1 channel inhibitor were examined by TAT-Panx-308.

**Results:** Non-invasively triggered CSDs induced para-inflammatory responses in both FHM1 and WT mice combined with increased mouse grimace scale scores and head grooming (HG)

I developed a novel method showing that non-invasively induced CSD triggers a para-inflammatory response that increases pain-related behaviour



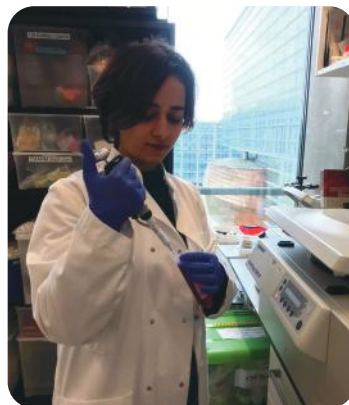
**The contribution of Panx1 channel activation to this inflammatory response and pain outcome highlights its key role in aura para-inflammatory profile and migraine headache leading to a potential therapeutic route to cure migraine**

**The IHS fellowship allowed me to work in the high-profile migraine research lab in Leiden**

but decreased nest building behaviours. In mutant mice, neuronal HMGB1 release was bilateral and prolonged (for 48 hours) following CSD in line with enhanced and prolonged higher scores of pain mimics and HG. Trigeminal ganglia were activated bilaterally after CSDs in both genotypes. CSD-related neuroinflammation and pain behaviour were blocked by inhibitor of Panx1 channels.



I developed a novel method showing that non-invasively induced CSD triggers a para-inflammatory response that increases pain-related behaviour; both stayed enhanced for a longer period in FHM1 mutant compared to WT. The contribution of Panx1 channel activation to this inflammatory response and pain outcome highlights its key role in aura para-inflammatory profile and migraine headache leading to a potential therapeutic route to cure migraine.



In my initial plan I aimed to do also RNA sequencing, but given the interesting results on HMGB1 release and pain mimics I instead increased the number of experimental groups to study the timing threshold for HMGB1 release and pain-related behaviour in both genotypes and genders. I also added another dimension of pain-related behaviour as HG and its different types such as oculotemporal strokes and laterality to investigate the importance of CSD effect on headache.

The IHS fellowship allowed me to have the opportunity to work in the high-profile migraine research group in Leiden which will be an enormous boost for my career in neuroscience, and particularly in the migraine field, and an

extremely important step for me in becoming a capable neuroscientist. By using the newest techniques related to optogenetics I have broadened my skills. The fellowship enabled me to investigate the pathophysiological mechanisms of migraine more efficiently and independently, and completion of the project with high-impact publications will provide more opportunities and chances in my career to gain funding for research. It also helped me to expand my network of scientists in different fields to perform future joint research and enabled me to participate in additional studies in the group because of my specific skills. I will remain in Professor van den Maagdenberg's group and do a follow-up study based on my research with the IHS fellowship.



The main purpose of the master class was to increase knowledge of headaches in Kyrgyzstan

120 delegates of varying specialities from different regions of the country attended

## Visiting Professor reports 1st Headache Master Class in Kyrgyzstan



Kunduz Karbozova

On 26-27 November 2019 the Headache Chapter of the Kyrgyz Scientific and Medical Society of Neurologists (KNMON), together with the Department of Neurology and Clinical Genetics named after A.M. Murzaliev of the KSMA I.K.Achunbaev, and with the support and auspices of IHS held the '1st Headache Master Class in Kyrgyzstan' with the invitation of leading specialists in the headache field, Sait Ashina, Associate Professor of the Department of Neurology and Anesthesia at Harvard Medical School, Boston, USA, and Vera Osipova, Scientific and Practical Center for Psychoneurology, Soloviev DZM and the University Headache Clinic, Moscow, Russia.



Vera Osipova

The main purpose of the master class was to increase knowledge of headaches, recognise primary forms of headache, improve the quality of care for patients and learn how to prescribe effective treatment.

This was the first meeting in Kyrgyzstan dedicated to headache medicine. Over 120 doctors from different regions of the country attended the master class, including paediatric and adult neurologists, family

doctors, therapists, pharmacologists, cardiologists and medical university teachers, clinical residents and students whose activities are related to the study, diagnosis, treatment, rehabilitation and prevention of headaches.

The master class was opened and welcomed by the Chairman of the KNMON, Academician of the National Academy of Sciences of the Kyrgyz Republic, Murzaliev Arstanbek and Head of the Department of Neurology and Clinical Genetics, Associate Professor Mamytova Elmira.

On the first day of the master class, a short test was conducted among the participants to assess their basic knowledge on headache medicine, after which Vera Osipova reported on the international classification and principles for diagnosing headaches. It is very important to note that not only in Kyrgyzstan, but also in Russia, there are problems with incorrect diagnosis of primary headache.



## Case presentations added an interactive element to the meeting

## The Kyrgyzstan doctors learned a lot of new information and increased their knowledge in the field of headache medicine

Sait Ashina presented a lecture on tension-type headache: how to correctly recognise the symptoms and how to properly diagnose and prescribe the necessary evidence-based treatment.

Assistant Professor of the Department of Neurology and Clinical Genetics of KSMA Kunduz Karbozova reported results of research work (within the framework of her PhD) on clinical characteristics of primary headache among patients who attended a headache specialist centre in Bishkek. Dr Karbozova also introduced the audience to the IHS mission and possibilities of IHS membership, which is free of charge to researchers and physicians from the Kyrgyz Republic.



Clinical case presentation and discussion

The first day concluded with a presentation of clinical cases of two patients with headaches; the invited professors had a conversation with the patients, collected their history and made recommendations for subsequent diagnosis and treatment.

During the second day Sait Ashina spoke about patient management of migraine, including the new monoclonal antibodies to CGRP (calcitonin gene-related peptide) therapies for the treatment of migraine. Vera Osipova shared her knowledge and experience in diagnosing and treating patients with chronic forms of primary headaches, and talked about the risks of chronicity and the burden of chronic headaches. She also taught about TACs and other headache and clearly identified the differentiation between the forms of TACs such as cluster headache, paroxysmal hemicrania, SUNCT and SUNA syndromes. Elmira Mamytova then gave a presentation on secondary headaches which are most commonly seen by family doctors and neurologists. Differential diagnosis and an algorithm of action were also clearly given to identify the secondary aetiology of headaches.

The final presentation by Sait Ashina was a lecture on the risk factors and treatment methods for medication overuse headache which arises from excessive use of drugs to relieve headaches, such as analgesics, triptans, NSAIDs, and opiates.



Sait Ashina and Kunduz Karbozova

Following the presentations, a second test was conducted among the participants, which showed excellent results compared to the pre-test, indicating the lectures, presentations and discussions had proved useful for the attendees. Thanks to the master class the doctors learned a lot of new information, improved their knowledge in the field of headaches, and received important practical assistance from the world's foremost specialists. Many attendees have indicated they would like to

organise more meetings and conferences in the headache field because it is very important to gain new knowledge from international headache specialists.

**450 delegates  
received updated  
information on both  
primary and  
secondary headache  
disorders**



I recommend that all young doctors interested in headache apply for an IHS Visiting Professor to attend a local meeting to give the opportunity for local neurologists and doctors to learn more about headache medicine, diagnosis and treatment.

On behalf of the Headache Chapter of KNMON and the Department of Neurology and Clinical Genetics named after A.M. Murzaliev at the KSMA I.K.Achunbaev, I express my gratitude to IHS, especially to the President Professor

Messoud Ashina for the huge opportunity, support and for helping to organise such a significant master class in our country. I express my gratitude to the Chair of the Education Committee, Allan Purdy, for providing and recommending the best international teachers for our master class, and to the lecturers, Sait Ashina and Vera Osipova for visiting our country, sharing their invaluable experience and giving very important advice to our doctors.

## Report of the 6th Iranian International Headache Congress



**Mansoureh Togha and  
Hossein Ansari**

The 6th Iranian International Headache Congress was successfully convened by the Iranian Headache Association from 16–18 October 2019 in Isfahan, Iran. This was the third Iranian International Congress held under the auspices of IHS. The congress was supported by the Iranian Neurological Association (INA).

Participants in the congress included 450 physicians, researchers and other healthcare professionals from all over Iran. Our IHS Visiting Professors were Jes Olesen from Denmark and Hossein Ansari from the USA. Parvin Allahyarova from Azerbaijan was another international invited speaker who discussed some challenging cases and participated in one of the panel discussions. Also for the first time, we used video conference where Sait Ashina from the USA delivered his presentation and Messoud Ashina, current President of IHS, delivered a video lecture and closed the conference during closing ceremony.

This scientific meeting provided updated information on most primary and some secondary headache disorders through various lectures and workshops. Attendees had an excellent opportunity to communicate with well-known national and international scientists in the field of headache.

**A mix of presentations and workshops on all aspects of headache was delivered by the international visitors and local experts**

**This congress was unquestionably able to play an important role in promoting the level of knowledge in the field of headache**



Jes Olesen

'Headache attributed to vascular disease' (M Saadatnia) and 'Medication overuse headache: is it an addiction?' (F Khorvash).

Thirty-nine Iranian speakers also presented lectures on a variety of headache and pain disorders including acute treatment of migraine headache, drug interactions in migraine treatment, non-medical therapies of headache, reversible cerebral vasoconstriction syndrome, treatment of trigeminal autonomic cephalalgias other than cluster headache, epidemiology and burden of headache disorders, neuroimaging in headache disorders, migraine with brainstem aura: defining the core syndrome, evaluation and management of headache in the emergency department, trigeminal neuralgia: MR imaging features, headaches and behaviour, and headache and epilepsy.

Abstracts of the lectures were available online on our website from the first day of the congress and an abstract booklet freely available to all participants upon registration.

In addition, there were a number of lectures on pain, neurostimulation techniques and various types of nerve blocks and pain injections presented by Iranian neurologists and 15 lectures on different headache topics were also delivered by young researchers during the congress.

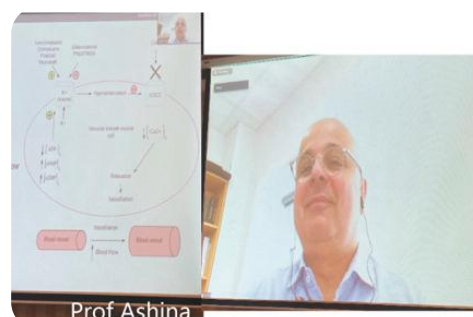
Three workshops were offered on Botulinum toxin injection for chronic migraine, peripheral nerve block in the treatment of headache, and neurosonology with emphasis on diagnosis of giant cell arteritis. All workshops involved live patient demonstrations and participants had the opportunity to have hands-on experience.

Three panel discussions also took place during the congress which explored management of trigeminal neuralgia, idiopathic intracranial hypertension; challenges in diagnosis and treatment and giant cell arteritis. This interactive panel was a new feature in this congress, and following positive feedback received from participants we will in future congresses increase the time for panel discussions.

Drs S Haghghi, H Hemasian and P Emami conducted a scientific competition with two teams in which 36 neurology residents from different medical universities of Iran participated.

Feedback from our international guests and participants was impressive and positive, commending the well-organised congress and highly interactive lectures. This headache congress was unquestionably able to play an important role in promoting the level of knowledge in the fields of

Several scientific programmes were held during the 3 days of the congress, and covered topics on 'Migraine aura and mimics' and 'Headache attributed to traumatic brain injury' (Jes Olesen), 'Facial pain: diagnostic considerations and role of neuroimaging' (Hossein Ansari), 'Targeting downstream mechanisms in migraine' (Messoud Ashina), 'What we know about CGRP in headache' (Sait Ashina), 'Presentation of interesting cases' (P Allahyarova), 'Update on management of cluster headache' (Mansoureh Togha),



IHS President Messoud Ashina delivers his lectures via video conference and closes the conference



Jes Olesen and Hossein Ansari with Mansoureh Togha, Chairman of IHA and some of the congress organisers

headache and pain in Iran. Additionally it increased awareness of healthcare providers about this important field. At the end of the congress, 57 new healthcare providers, the majority of them neurologists, registered as members of the Iranian Headache Association.

The attendance of distinguished international headache specialists with the cooperation of IHS, and communication between them and the esteemed Iranian neurologists and active participants from all over Iran in response to the invitation of the Iranian Headache

Association, has paved the way to establish a good link between the Iranian Headache Association and IHS. Future collaboration will surely help the advancement of the headache field in Iran and even further within our geographical region.

## Latin America Master School 2019



Michel Volcy

The Latin America Master School took place in Bogotá, Colombia, from 3–5 October 2019 at the NH Hotel Collection. The event was the culmination of many months of work by the Colombian Neurology Society committee (Joe Muñoz, Fidel Sobrino, Bernardo Uribe, Sergio Ramirez, Oscar Pradilla and Michel Volcy as leader and Coordinator) in collaboration with Mario Peres, and Allan Purdy, IHS Education Committee Chair, whose strong guidance, patience and assertiveness was of great value.

Following completion of the Master School, all attendees who achieve 70% over the three mandatory written examinations (before, at the end of the course and 6 months after) will be given a certificate.

Faculty members included Cristina Tassorelli, Italy, Andrew Charles, USA, Manjit Matharu, UK, Jose Miguel Láinez, Spain, Maria Teresa Goicochea, Argentina, Federico Buonanotte, Argentina, and the organising committee members.

The course welcomed 105 participants from Colombia (75), Argentina (7), Peru (4), Mexico (6), Chile (11) and Bolivia (2). Following an



105 participants from  
6 Latin American  
countries attended



**Only 5,000  
neurologists in Latin  
America serve  
around 626 million  
inhabitants**

opening welcome video from Allan Purdy, the programme proceeded with a mixture of lectures in plenary sessions, case-based plenary activities, controversy sessions and a special interactive session during which the international speakers were interviewed on their experiences as headache specialists and why they would recommend it as an important field to work in.

Two sets of exams each containing 30 questions took place during the master school, the first after the introduction and methodology explanation, the second on the last day of the academic sessions.



Sergio Ramirez, Miguel Láinez, Federico Buonanotte, Manjit Matharu, Fidel Sobrino, Cristina Tassorelli, Michel Volcy, Andrew Charles, Maria Teresa Goicochea, Mauricio Rueda

The Latin-American population currently is about 626,000,000 (Wikipedia November 2019) in 20 countries; the estimated number of neurologists is around 5,000. Some neurologists are headache experts educated abroad; very few headache fellowships are offered in Latin-American countries which leads to a lack of well trained headache neurologist experts. This was the second Latin-American Master School (the first in Brazil in 2011–2012) and there is a need for continued headache education programmes in the region in the coming years.



Oscar Pradilla and Michel Volcy



Cristina Tassorelli



This was one of the best academic and social experiences of my career

During the programme I attended IHC in Dublin and the 50th anniversary meeting of the Danish Headache Society

## Headache Trainee report



Khatia Gvantseladze,  
Georgia

**Danish Headache Centre, Copenhagen, Denmark**  
**Mentor: Messoud Ashina**

First of all, I would like to thank IHS for giving me this amazing opportunity to develop myself as a clinician. I would like to offer my absolute appreciation to the Danish Headache Centre with its brilliant team and all the people I interacted with during my stay there for almost 3 months. This was one of the best academic and social experiences of my career development.

During my time at the Danish Headache Center, I undertook both clinical and scientific activities. I attended the rotations of the patient examinations together with the clinical team of the centre; they shared their experiences and discussed the twists of the newest approaches to patients with headache, some difficult clinical cases, and also demonstrated



The Danish Headache Center Team

theoretical knowledge in headache treatment procedures, such as Botox, GON block, etc. I have witnessed how a specialised headache centre is regulated at all levels and what an important role the great team plays. I was also introduced to how the science is done at the Danish Headache Center; I was assigned to the migraine group project and worked on a scientific paper, 'The stereotypical image of a migraine patient according to mass media'. This was one of the most interesting and challenging experiences of my career.

During the Trainee Programme I was also privileged to attend the IHC 2019 in Dublin, Ireland, with the Danish Headache Center team. This was an unforgettable professional and

**I will work to develop  
headache practice  
throughout the whole  
of Georgia**



Frederiksborg Castle, Copenhagen, Denmark

social experience for me. I also attended the Annual Meeting of the Danish Headache Society, the 50th anniversary, held in Copenhagen.

Visiting the Danish Headache Center has more than met all my initial aims professionally, as well as personally. The traineeship introduced me to professional aspects I haven't experienced before, hence refining my knowledge, clinical skills, mindset and starting to perceive things from different viewpoints. I have grown a lot as a professional and started to think wider about the possible opportunities for my further career development. Now, while leading the neurology department at one of the biggest hospitals in Tbilisi, Georgia, also having a private practice at the ambulatory service, I will try to develop the headache field more and share my entire experience in practical ways. My mentor, Professor Zaza Katsarava, who is the biggest support I have, and I are already trying to develop headache practice not only in Tbilisi, but throughout the whole of Georgia. I'm sure this international experience will play its role for the big plans and hope this won't be the last platform for gaining international experiences in the future.

I would like to once again express my sincere appreciation and gratitude to Professor Ashina and the whole Danish Headache Center team who welcomed me from the very beginning and made me feel part of the big headache family. Professor Messoud Ashina is a real master of his work, a team leader, mentor and colleague, and supported me at every point and shared his priceless experience, which helped me to become a better clinician and person, to think further and deeper and dream big.



Copenhagen "Neuro Cup" Competition

International Headache Society, thank you for everything! And thank you for that emotional feeling I was having while updating my report and remembering the best international experience I have had so far, by means of your help!



International  
Headache Society

## IHS Fellowship Awards 2020

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**APPLY NOW** if you are interested in enrolling in one of these international programmes

**12-month award value: £ 50,000**

Fellowship Award open to IHS members

**Deadline: 1 July 2020**

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IHS is an international professional organisation working with others for the benefit of people affected by headache disorders. As a charity, the purpose of IHS is to advance headache science, education, and management, and promote headache awareness worldwide.

Visit the IHS website for more information and an application form

**[www.ihs-headache.org](http://www.ihs-headache.org)**



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**Susie Lagrata, Headache Nurse (Graduate)**

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## Calendar of events

### 2020

23-26 May	6th Congress of the European Academy of Neurology	Paris, France	<a href="#">Visit website</a>
4-7 June	62nd Annual AHS Scientific Meeting	San Diego, USA	<a href="#">Visit website</a>
3-5 July	14th European Headache Federation Congress	Berlin, Germany	<a href="#">Visit website</a>
4-8 August	2020 World Congress on Pain	Amsterdam, Netherlands	<a href="#">Visit website</a>
10-13 September	18th Migraine Trust International Symposium	London, UK	<a href="#">Visit website</a>

**Important note:** Events may be cancelled or postponed due to coronavirus pandemic - please check each event website for updated information

If you would like IHS to include your meeting on the IHS website and newsletter please contact **Carol Taylor** with the details





## New Open Access companion journal for Cephalalgia

### Cephalalgia Reports: A fully Open Access Journal

Published on behalf of the International Headache Society, *Cephalalgia Reports* is a peer-reviewed, open access publication providing an international forum for original research papers, review articles, clinical perspectives, technical reports and short communications.

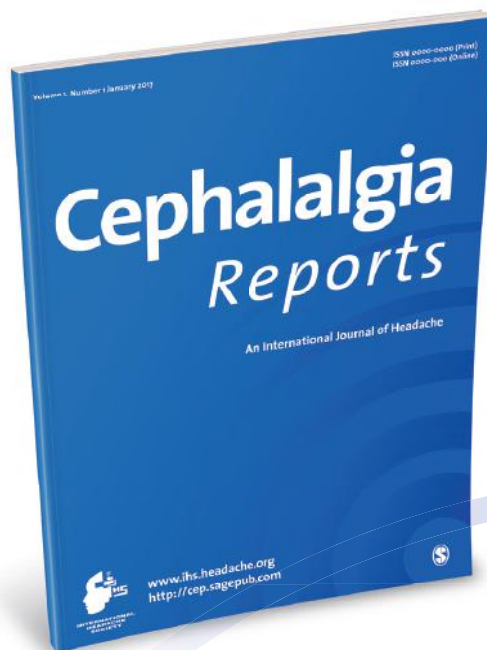
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To advance headache science, education and management  
and promote headache awareness worldwide

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