The prevalence and disability associated with migraine and other headache disorders has come under a spotlight in an unprecedented way. The recently published Global Burden of Diseases report identified tension-type headache and migraine as the 2nd and 3rd most prevalence medical illnesses worldwide. Furthermore, migraine accounts for 30% of the global burden of disease, and more than 50% of the disability burden attributable to all neurological disease worldwide. Overall, it is the 4th leading cause of disability among women and 7th ranking cause of all disease-associated disability worldwide.

Over the past year there have been advances in the genetics of migraine with genome-wide association studies uncovering a number of susceptibility genes for common migraine subtypes. Similar to biological consequences of the autosomal dominant mutations of familial hemiplegic migraine, many of these susceptibility genes may result in increased neuronal and glial excitability as a result of alterations glutamate transport. Other genes involved in pain signaling and endothelial and vascular function may play a role in some migraine endophenotypes.

There has also been forward progress has been made in the understanding of the pathophysiology of migraine and the potential mechanisms by which the symptoms of migraine become chronic, persistent, and more resistant to treatment. The site of origin of migraine without aura has long been a source of debate and uncertainty. A recent PET study during the premonitory phase of migraine identified activation within the hypothalamus, midbrain and pons during early and late phases of the premonitory phase which precedes pain/headache. Activation or dysfunction within these subcortical regions could well explain many of the symptoms that characterize the premonitory phase. With regard to migraine with aura, the potential mechanisms by which cortical spreading depression may activate peripheral and central trigeminal sensory neurons is being unraveled and this new information identified new molecular and receptor targets for drug development.

The structural and functional changes that occur in the brain as a result of frequent attacks of migraine over time have also become evident using functional and quantitative MRI. The somatosensory, cingulate and insular cortex appears to undergo functional and structural changes that may explain the persistence (and memory) of pain. Resting state functional connectivity MRI has also demonstrated enhanced sensory processing within functionally connected brain regions that process emotional, light, sound, and pain (as well as pain relief) which explains the persistence of associated symptoms and comorbid mood disorders that are prevalent in patients with chronic migraine.
Important new knowledge in the epidemiology of migraine and vascular risk was recently presented at the American Academy of Neurology in San Diego. Based on the a prospective cohort study of 27,860 women aged ≥45 participating in the Women's Health Study, migraine with aura was shown to be strongest single contributor to ischemic stroke relative to other vascular risk factors, including diabetes and hypertension. This has profound implications for risk stratification, treatment, and counseling in clinical practice as well as the need for more detailed research into the mechanism(s) underlying this association and whether preventive treatment of migraine with aura influences the risk of stroke. An important prospective 9-year follow up of the seminal CAMERA study in the Netherlands demonstrated that women with migraine had higher volumes and greater progression of deep white matter hyperintense lesions, but not brainstem white matter hyperintense lesions or posterior circulation infarctions (although 5% of the migraine subjects developed new cerebellar infarctions compared to 0 in the control group). Lesion load was not related to the type (aura or non-aura) nor frequency of attacks, and there was no evidence that the progression of white matter hyperintense lesions was associated with the development of cognitive impairment.

Finally, while the migraine and headache field overall has only ever seen one drug class ever designed and approved specifically for migraine (triptans), randomized controlled trials using several different peripheral neurostimulation options for drug-resistant primary headache disorders have shown positive and/or promising results. Single-pulse transcranial magnetic stimulation is now approved in the UK and sphenopalatine ganglion stimulation has shown early promise for the treatment of cluster headache. Controlled trials evaluating the efficacy of implanted occipital stimulation leads have failed to reach their primary endpoint. However, phase III trials are about to begin based on promising results on multiple secondary endpoints and a better understanding of the clinical features that may predict efficacy.

A number of viable and novel molecular and receptor targets have emerged for the acute and preventive treatment of migraine. These targets include neuronal nitric oxide synthase (nNOS) as well as multiple receptor targets including the delta opioid, orexin, metabotropic glutamate, acid-sensing ion channel type III (ASIC-3), calcitonin gene-related peptide (CGRP), and 5-HT1F receptors. The targets furthest along in clinical development include the elective 5HT1F agonists and CGRP receptor antagonists.

Lasmiditan, a highly selective 5-HT1F receptor agonist has demonstrated efficacy in two randomized placebo-controlled trials. This mechanism of action has advantages over the triptans and ergots because of a lack of 5-HT1B activity and therefore, the potential to result in vasoconstriction. CGRP receptor antagonists have proven effective in the acute treatment of migraine, and like the 5HT1F agonists, CGRP receptor antagonists lack vasoconstrictor activity and therefore do not share the vascular liability associated with the triptans and ergots. While hepatotoxicity terminated the development of initial oral drugs which showed promising efficacy results, the results from phase II acute trials with novel CGRP receptor antagonists will soon be reported and monoclonal antibodies against either the CGRP molecule or its receptor have entered phase II prevention trials. The importance of CGRP in the pathogenesis of migraine, along with the selectivity and lack of off-target biology of monoclonal antibodies, provides optimism for a novel prevention mechanism with a safe, well-tolerated, and highly specific drug class.
References:


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