Headache 2
The pathophysiology of migraine: implications for clinical management

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The understanding of migraine pathophysiology is advancing rapidly. Improved characterisation and diagnosis of its clinical features have led to the view of migraine as a complex, variable disorder of nervous system function rather than simply a vascular headache. Recent studies have provided important new insights into its genetic causes, anatomical and physiological features, and pharmacological mechanisms. The identification of new migraine-associated genes, the visualisation of brain regions that are activated at the earliest stages of a migraine attack, a greater appreciation of the potential role of the cervical nerves, and the recognition of the crucial role for neuropeptides are among the advances that have led to novel targets for migraine therapy. Future management of migraine will have the capacity to tailor treatments based on the distinct mechanisms of migraine that affect individual patients.

Introduction
The ongoing Global Burden of Diseases, Injuries, and Risk Factors Study continues to identify migraine as a leading cause of disability worldwide, particularly in individuals younger than 50 years. Notably, disorders that are commonly comorbid with migraine, including neck pain, depression, and anxiety, are also among the top ten causes of disability worldwide, placing migraine in a central position among the world’s most disabling disorders. Furthermore, medication overuse headache is now one of the top causes of disability worldwide. The overlap between migraine and several other commonly disabling disorders indicates that they might have common mechanisms; improved understanding of these shared mechanisms could inform the clinical management of the diseases that cause a substantial proportion of the world’s leading disability.

Much progress has been made in the understanding of migraine, which has created new opportunities for more effective management of patients. In this Series paper, I describe the most recent advances in genetics and pathophysiology, and their implications in the management of patients with migraine.

Classification and diagnosis
The International Classification of Headache Disorders (ICHD) remains an invaluable resource for criteria for the diagnosis of migraine. The evolution of this classification system reflects a growing understanding of the heterogeneity of headache disorders and their variable clinical presentations. Several important revisions regarding migraine diagnosis have been made in the most recent iteration of the ICHD (ICHD-3 beta). For example, using the ICHD-2 criteria, patients needed to have 15 migraine headache days per month in the absence of medication overuse to receive a diagnosis of chronic migraine. ICHD-3 beta now specifies that patients must have 15 headache days per month, but migraine-associated features are required on only 8 of these 15 headache days, and that medication overuse can exist concurrently with a diagnosis of chronic migraine.

This parsing of headache days with or without migraine features illustrates how migraine diagnosis can be confounded by the variability of attack features from person to person and from attack to attack in the same individual. Patients with migraine commonly report that they have more than one type of headache, with each type having considerably different clinical features. For example, prospective recording of symptoms indicates that the occurrence of premonitory symptoms, nausea, and aura can be highly variable in an individual. Medication overuse can introduce additional variability, and approximately 50% of patients with chronic migraine revert to episodic migraine after drug withdrawal. Individual migraine attacks with different clinical characteristics might respond differently to acute or preventive therapies; thus, recording such variability in clinical features and medication use could be particularly important in analysis of clinical trial data in which nausea or aura symptoms are the defining features of migraine attacks, as well as in epidemiological studies in which patients are classified as having only one diagnosis (such as migraine with aura vs without aura, or chronic migraine vs medication overuse headache). The development of genetic, biochemical, and imaging biomarkers could, in combination with detailed characterisation of clinical features, lead to a more accurate diagnosis of migraine and a better ability to predict an individual patient’s response to different therapies.

Another important change in the ICHD-3 beta criteria is their updated approach to diagnosing vestibular symptoms, including vertigo and dizziness, which are common features of a migraine attack. These symptoms were previously included as part of the diagnosis of basilar migraine, which has been replaced by the diagnosis of migraine with brainstem aura. The different nomenclature is in part an acknowledgment of...
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This change in classification raises questions about the contraindication for the use of triptans in basilar migraine, which was based on the probably incorrect presumption that these symptoms were caused by constriction of the basilar artery that could be compounded by the vasoconstrictive action of triptans. Indeed, a magnetic resonance angiography study found that administration of sumatriptan to 19 patients during a migraine attack resulted in only 2% constriction of the basilar artery on average, a clinically insignificant vasoconstriction. The effort to emphasise that although vasodilation is not the cause of migraine headache, vascular mechanisms might nonetheless have an important role in the pathophysiology of migraine. Another population study found that genetically mediated hypercalcaemia over the lifetime is associated with an increased risk of migraine. The complex range of potential genetic mechanisms that lead to migraine raises the possibility that therapy could eventually be tailored to specific genetic mechanisms responsible for migraine in individual patients.

Pathophysiology

Phases of a migraine attack

A migraine attack can be divided into phases on the basis of its temporal relationship to headache: the premonitory phase (precedes headache), the aura phase (immediately precedes or accompanies headache), the headache phase, the appendix of ICHD-3 beta, which describes new disorders that need further validation. Depending on other associated symptoms, migraine-associated vertigo can now be classified either as vestibular migraine or migraine with brainstem aura. Regardless of the classification, migraine is commonly associated with episodic vertigo. An increased understanding of how migraine leads to derangements of vestibular function will enable better diagnosis and management of patients with episodic vertigo.

Genetics

Although migraine is commonly familial, genome-wide association studies have not yet identified any genetic alterations with large effect sizes. Single gene mutations have been found in rare migraine syndromes, including familial hemiplegic migraine and monogenic vasculopathies, as well as in individual families. Two genetic mutations associated with migraine identified in two families are in the gene encoding the enzyme casein kinase 1δ (CK1δ). These mutations are also associated with familial advanced sleep phase syndrome, a circadian rhythm disorder in which sleep onset and awakening from sleep are shifted to earlier hours. This disorder is considered to be rare; however, it could be under-reported as a migraine-associated disorder because patients might adapt well to the symptoms and therefore not seek medical attention.

38 genomic loci associated with migraine have been validated in population studies. The large number and functional diversity of these genes underscore the complexity of the genetic contribution to migraine and the likelihood that, in most cases, migraine involves interaction between multiple genes and epigenetic factors (figure 1). Loci associated with migraine were found to be enriched in genes that are expressed in vascular and gastrointestinal tissue, and several gene sets associated with vascular biology (including wound healing and cell–cell interaction) were significantly enriched for loci containing migraine-associated genes. These findings emphasise that although vasodilation is not the cause of migraine headache, vascular mechanisms might nonetheless have an important role in the pathophysiology of migraine. Another population study found that genetically mediated hypercalcaemia over the lifetime is associated with an increased risk of migraine. The complex range of potential genetic mechanisms that lead to migraine raises the possibility that therapy could eventually be tailored to specific genetic mechanisms responsible for migraine in individual patients.

Figure 1: Contributing factors and mechanisms of a migraine attack

A wide range of factors can contribute to the initiation of an attack, with variable mechanisms leading to a migraine attack. The clinical features of a migraine attack then diverge on the basis of genetic, anatomical, and other factors. CGRP=calcitonin gene-related peptide. PACAP=pituitary adenylate cyclase-activating polypeptide.

Factors

- Genes
  - >38 migraine-associated gene polymorphisms

- Environment
  - Barometric pressure
  - Stress

- Metabolism
  - Diet
  - Neuroendocrine function

- Hormones
  - Menstrual cycle
  - Pregnancy

- Drugs
  - Exacerbating medications

Mechanisms

- Hypothalamic activation
- Alteration in thalamo-cortical circuits
- Altered brain connectivity
- Brainstem activation
- Cortical spreading depolarisation
- Release of CGRP and PACAP

Migraine attack

- Migraine genes
- Hormonal and metabolic state
- Cervical nerve anatomy
- Drugs

Variable attack symptoms and severity: premonitory, aura, headache, and postdrome phases

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Pathophysiology

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A migraine attack can be divided into phases on the basis of its temporal relationship to headache: the premonitory phase (precedes headache), the aura phase (immediately precedes or accompanies headache), the headache phase,
and the postdrome phase (after resolution of headache). Although this description of a migraine attack is practical, the phases of an attack can be overlapping and variable. Some symptoms of a migraine attack (sensory sensitivity and neck pain) might be present throughout an attack, whereas others (aura symptoms) might come and go. The different phases of a migraine attack represent an opportunity to characterise and distinguish the physiological changes that are occurring at the start of a migraine attack, those that are responsible for headache, and those involved in the process of recovery (figures 1, 2).

In the premonitory phase, a variety of symptoms, including yawning, polyuria, mood change, irritability, light sensitivity, neck pain, and concentration difficulties, among others, commonly occur hours before onset of headache during a migraine attack. Although some of these symptoms are subjective, others, particularly sensory sensitivity, can be objectively quantified. For example, changes in quantitative sensory thresholds occur hours before headache, consistent with the occurrence of subjective sensory symptoms in the premonitory phase. PET and functional MRI studies of triggered and spontaneous migraine attacks show changes in the activity and connectivity of the hypothalamus in the hours preceding headache. These changes in hypothalamic function could be responsible for polyuria, mood change, and change in appetite preceding headache. PET studies of the premonitory phase also show that increased activity in the occipital cortex is correlated with light sensitivity, and that activation of the brainstem is correlated with nausea.

### Thalamic and thalamo-cortical circuits

Electrophysiological studies show changes in brain function in the premonitory phase, particularly in the circuits that connect the thalamus and the cortex. Furthermore, structural and functional imaging studies show differences in thalamic and thalamo-cortical activity in patients with migraine versus control groups both during and between migraine attacks, and studies have implicated the thalamus as an important mediator of cutaneous allodynia and exacerbation of headache by light. Taken together, these studies provide strong evidence that changes in thalamic and thalamo-cortical activity play a key part in the aberrant sensory processing that is a central feature of a migraine attack, and could represent a therapeutic target for pharmacological and neuromodulatory approaches such as transcranial magnetic stimulation.

### Network connectivity

Several studies have used resting-state MRI to investigate changes in the connectivity of different brain regions before and during migraine attacks. These studies showed altered connectivity of the cortex, thalamus, hypothalamus, brainstem, amygdala, and cerebellum, consistent with changes in the function of multiple overlapping sensory and pain-processing circuits, and circuits involved in anxiety and mood. Although the consequences of these changes in connectivity remain uncertain, they might be involved in the modulation of pain and sensory sensitivity that occurs both ictally and interictally in patients with migraine. Cognitive dysfunction is another common symptom of migraine and a cause of disability associated with migraine attacks, that could be related to disruptions of normal brain functional connectivity. A coherent pattern of changes in brain connectivity in migraine has yet to emerge; however, these resting-state studies confirm that migraine involves widespread alterations in brain function.

### Neck pain

Neck pain is a common symptom of migraine that can begin in the premonitory phase and continue through the postdrome phase, and might be an important...
contributor to migraine-related disability. Causative structural pathology of the cervical spine is rare, but the frequent occurrence of neck pain could indicate a role for the upper cervical nerves in the transmission of migraine pain. Pain inputs from the cervical nerves converge with those from the trigeminal nerve on the second-order neurons in the brainstem and upper cervical spinal cord. In individuals with or without migraine, stimulation of the cervical nerves triggers head pain, whereas C1 stimulation in patients with migraine triggers pain in a peri-orbital distribution. This referral pattern could be due to central sensitisation of the trigemino-cervical complex, where cervical and trigeminal inputs converge. Another contributing factor could be anatomical variation of the upper cervical nerve roots. Anatomical studies indicate considerable variability of the structure and anastomoses of the upper cervical nerve roots, particularly the C1 root in human beings. This variability raises the intriguing possibility that structural differences in the cervical nerve roots could influence the pattern of migraine pain (including headache), and particularly its response to local therapies such as suboccipital injections of local anaesthetics and steroids. A nerve-tracing study showed that branches of the trigeminal nerve can reach the neck musculature through the skull, suggesting a possible role for trigeminal afferents in migraine-related neck pain.

Aura

The clinical significance of migraine aura and its underlying mechanisms continue to be topics of active investigation. Population studies indicate that a diagnosis of migraine with aura is associated with an increased risk of other comorbidities, such as patent foramen ovale, ischaemic stroke including perioperative stroke, restless legs syndrome, Parkinson’s disease, bipolar disorder, and panic disorder. As with other migraine symptoms, the occurrence of an aura during a migraine attack is variable for most patients, and the clinical features of the aura itself might also vary considerably in an individual over nearly two decades has provided important insights into the initiation and propagation of the aura phenomenon in the visual cortex. In this individual, the location of onset of the aura within the visual field was variable, the characteristics of the visual percept changed from a positive wave front to a negative scotoma as the aura progressed, and during certain times the aura was apparently progressing but no visual change was perceived. These observations indicate that the physiological phenomenon underlying the aura might have multiple foci of onset within the visual cortex, that the clinical features of the visual aura correspond to the specific regions of the visual cortex through which this phenomenon is propagating, and that the aura phenomenon might be clinically silent in certain regions of the cortex. In rodents, which have lissencephalic brains that lack the sulci and gyri of the human brain, cortical spreading depolarisation propagates as a concentric wave that commonly involves the majority of one hemisphere. In representations of human brains, it is often similarly depicted as a broad, concentric wave that traverses multiple sulci and gyri. However, mapping the visual aura onto models of the human visual cortex indicates that the physiological phenomenon that causes the migraine aura travels in a much more spatially limited and linear manner along single gyri and sulci, similar to the pattern that is observed in recordings of spreading depolarisations in patients with brain ischaemia or traumatic injury. A long-standing hypothesis is that the aura is a primary initiator of a migraine attack, leading to headache and other migraine symptoms. This hypothesis is based in part on work in animal models, in which cortical spreading depolarisation (which was previously described as cortical spreading depression), believed to be the physiological substrate of the migraine aura, was shown to activate pain signalling via both peripheral trigeminal and central descending pathways. Whether cortical spreading depolarisation and migraine aura cause headache in human beings, however, remains controversial. Migraine aura commonly occurs without headache, and most migraine attacks do not include aura, indicating that the aura is not necessary or sufficient for headache. Prospective patient reporting of migraine attack features also reveals that a majority of patients might have headache as well as other defining migraine symptoms, including light sensitivity and nausea, at the time of aura onset, raising questions about the role of aura mechanisms as initiators of these symptoms. An alternative hypothesis is that cortical spreading depolarisation represents just one component—not necessarily the primary component—of the widespread and variable dysfunction of the nervous system that comprises the aberrant brain state of a migraine attack. Cortical spreading depolarisation in rodents is associated with brain tissue swelling and has been reported to cause closure of perivascular spaces, a phenomenon that is hypothesised to impair the physiological clearance of solutes. The relevance of this phenomenon to migraine remains uncertain given the major differences between cortical spreading depolarisation in the lissencephalic rodent cortex and in the gyrencephalic human cortex, as well as the fact that...
migraine aura can occur repetitively and frequently over a lifetime with no clear deleterious effects on brain structure or function.60

Neuropeptides as mediators of migraine
Accumulating evidence indicates a primary role for calcitonin gene-related peptide (CGRP) as a mediator of migraine and as an important therapeutic target. Studies have shown that CGRP is released into the circulation during a migraine or cluster headache attack, and that its concentration normalises with triptan therapy but not with a non-specific opioid analgesic.67 CGRP concentrations have been reported to be persistently elevated in patients with chronic migraine.68 Infusion of CGRP triggers delayed migraine in susceptible individuals,69 and several small-molecule CGRP antagonists have shown efficacy as acute migraine therapies.70,71

The evidence for pituitary adenylate cyclase-activating polypeptide (PACAP) as a mediator of migraine parallels that for CGRP. Like CGRP, systemic administration of PACAP triggers migraine in susceptible individuals,72 and elevated concentrations of PACAP have been reported in patients with migraine during attacks.73 Generalised flushing and sustained vasodilation are common responses to administration of PACAP, whereas these responses do not occur as prominently with CGRP.74 Therefore, PACAP, like CGRP, represents a promising therapeutic target in migraine, and future therapeutic approaches targeting PACAP will validate whether it is also an important mediator of migraine.

Management
Effective clinical management of migraine requires recognition and elimination of specific exacerbating factors, and personalisation of acute and preventive treatment approaches.

Lifestyle factors
Consistency of diet, an adequate amount of sleep, consistent caffeine intake, and regular exercise are all approaches to reduce migraine frequency and severity, although no high-quality research has supported the efficacy of these approaches yet. Patients with migraine often focus on identifying dietary triggers for their attacks, but no high-quality evidence exists to support the efficacy of any specific elimination diet.78 Instead, patient-identified triggers could be a reflection of symptoms that are occurring at the earliest stages of a migraine attack; sensitivity to light, sound, or smell might precede headache during a migraine attack, leading patients to the conclusion that bright light, loud sounds, or strong smells are triggers rather than symptoms of the premonitory phase.79

Exacerbating medications
Various medications might exacerbate migraine. The frequent use of acute migraine medications can be associated with worsening of migraine, and the ICHD-3 beta78 has established different numerical thresholds for the diagnosis of different types of medication overuse headache. Medication overuse is classified as at least 10 days per month using ergotamines, triptans, combination analgesics, or opioids for at least 3 months, and at least 15 days per month using simple analgesics (eg, non-steroidal anti-inflammatory drugs and paracetamol) for at least 3 months. This designation is controversial, particularly given that the so-called tipping point for medications as a risk factor for transition from episodic to chronic migraine is as few as 5 days per month for barbiturates (butalbital complex) or 8 days per month for opioids.79 Indeed, each of the acute medications potentially causing medication overuse appears to have a different profile in terms of its risk of causing progression of migraine.79
Further studies are needed to generate evidence-based guidelines for appropriate limits for the use of acute migraine medications.

Medications taken for other indications might also worsen migraine. Oral contraceptive preparations, post-menopausal hormone replacement, decongestants, selective serotonin reuptake inhibitors, and proton-pump inhibitors are among the commonly prescribed medications that are observed anecdotally in clinical practice to worsen migraine. The scarcity of data on this topic is surprising, given how common the exacerbation of migraine by other medications can be. Prospective studies to obtain such data are unlikely to be done, but high-quality population data from registries could have the potential to delineate the adverse effects of different medications on migraine frequency and severity.

Acute treatment
The overall pharmacological approach to the management of acute migraine has not changed much since 2012. Triptans, non-steroidal anti-inflammatory drugs, and antiemetics continue to be the mainstays of acute migraine therapy.10 Different non-oral and oral preparations of triptans and non-steroidal anti-inflammatory drugs have been developed (nasal sprays, different injection preparations, transdermal patches, and oral powder formulations). Efficacy might be improved because of the more rapid onset of action than that of existing medications and, in the case of non-oral preparations, because they avoid the issue of impaired gastrointestinal absorption during migraine attacks.12 Administration of acute migraine therapy as early as possible within a migraine attack remains an important principle for optimisation of efficacy. An interesting question that arises from the increased recognition—by both patients and researchers—of premonitory symptoms is whether acute treatment during the premonitory phase could result in even greater efficacy for some patients.

Nausea
Nausea is a highly disabling symptom on its own, and therefore the relationship between migraine-associated nausea and greater disability is not surprising.13 Patients commonly have nausea with some, but not all, of their attacks,14 and migraine-associated nausea is generally undertreated. Severe nausea is associated with reduced therapeutic efficacy of intravenous dihydroergotamine in the inpatient setting,15 and a population-based study15 indicated that persistent frequent nausea is a risk factor for progression of migraine, suggesting that effective treatment of nausea could improve both short-term and long-term outcomes of migraine therapy. Accumulating evidence supports the efficacy of dopamine receptor antagonists, which are generally thought of as antiemetic therapies, as acute migraine therapies. Phenothiazine and metoclopramide antiemetic therapies were efficacious as treatment for migraine in the setting of the emergency department.16 The substance P antagonist aprepitant has been reported to be effective in the therapy of nausea associated with administration of dihydroergotamine17 and for cyclic vomiting syndrome in children.18 Thus, substance P antagonists might be effective in the treatment of migraine-associated nausea.

Migraine aura
Compared with migraine without aura, attacks with aura might be less responsive to triptans and might also have a differential response to preventive therapies.19 Currently, no evidence-based treatment for migraine with aura is available, although results from a clinical trial of ketamine for prolonged aura suggest that glutamate receptor antagonists might be effective.20 Migraine with aura seems to be related to stroke, potentially through the association between migraine aura and right-to-left shunt in the systemic circulation, including that caused by patent foramen ovale.21,22 Thus, medications that cause hypercoagulability (eg, oral contraceptives) could increase the risk of stroke due to an increased risk of paradoxical embolism.23 However, most data regarding stroke risk with oral contraceptives were obtained when oestrogen doses in these preparations were much higher than they are currently. Similarly, no evidence exists indicating that triptan use should be contraindicated in patients with migraine with aura.

Preventive treatment
As with acute therapies, little overall change has occurred in migraine preventive therapy since 2012. Beta blockers, tricyclic antidepressants, anticonvulsants including topiramate and valproex sodium, onabotulinum toxin A (for chronic migraine), and flunarizine (outside the USA) continue to be standard therapies for migraine prevention.24,25 A randomised placebo-controlled study26 of candesartan as an effective preventive therapy in 72 patients with migraine has led to increasing use of this treatment, particularly because of its generally excellent tolerability. Unfortunately, clinical criteria or biomarkers that predict which specific preventive therapy might be most effective for an individual patient are not available, and the choice of preventive therapy is therefore often based on tolerability or comorbid conditions.

Injections of local anaesthetics with or without steroids, particularly in the region of occipital nerves, are routinely done in headache centres as preventive therapy for patients with migraine. These procedures are often described as nerve blocks, although blockade of nerve sensory function as evidenced by anaesthesia in the distribution of the nerve might not be required for therapeutic efficacy. Clinical experience indicates that these procedures are particularly beneficial for patients with very frequent migraine or status migrainosus. An observational study27 and clinical experience have indicated that tenderness over the occipital nerve and forward radiation of pain on pressure over the occipital

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nerves are predictors of benefit from occipital injections. Results from randomised placebo-controlled studies have been mixed: one study of 69 patients with episodic or chronic migraine showed no benefit, whereas two studies of 84 and 36 patients with chronic migraine did show benefit. Positive responses to occipital nerve injections were also reported in patients with prolonged or persistent migraine aura, as well as in those with triptan overuse headache. Because the occipital nerve is believed to be composed primarily of C2 and C3 afferents, occipital injection could therefore miss the C1 nerve, which is also a potential modulator of migraine pain. Occipital nerve injections are relatively easy to do, with low complication rates and, thus, are a reasonable approach to try in selected patients, despite mixed supporting evidence. Clinical trials with refinement of predictive clinical criteria would be helpful in guiding appropriate use of occipital injections in the future.

Conclusions and future directions
The pace of progress in the understanding of migraine is accelerating rapidly, and the direct translation of the results of basic migraine research into new treatments that specifically target migraine mechanisms is particularly gratifying. Improved understanding of genetic factors underlying migraine has the potential to tailor therapies to individuals with different genetic backgrounds. Characterisation of the premonitory phase of a migraine attack and its underlying mechanisms provides an opportunity to treat a migraine attack at its very earliest stages, and could reveal new therapeutic targets, such as the hypothalamus. Neuromodulation approaches could enable physicians to specifically target novel central and peripheral migraine mechanisms, such as alterations in thalamo-cortical circuits, or contributions of cervical nerve roots to migraine headache. The recognition of the key roles for neuropeptides, including CGRP and PACAP, and the development of therapies targeting these peptides or their receptors represent a promising new approach to migraine treatment. Now is a crucial time to maintain the momentum that has been established by recent basic and clinical research, and push forward towards safe, efficacious, and individualised care for patients with migraine.

Search strategy and selection criteria
References were identified by searches of PubMed between Jan 1, 2012, and Aug 31, 2017, and references from relevant articles. The search terms “migraine”, “diagnosis”, “disability”, “genetics”, “pathophysiology”, “PET”, “MRI”, “electrophysiology”, “pharmacology”, “premonitory”, “aura”, “postdrome”, “therapy”, “treatment”, “CGRP”, and “PACAP” were used. I did not apply any language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this Series paper.

Declaration of interests
I have served on advisory boards for Alder BioPharmaceuticals, Biohaven, eNeura, and Eli Lilly, as a compensated consultant for Amgen, as a symposium speaker for Amgen and Eli Lilly, and received grant support from Takeda.

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