RESIDENT & FELLOW SECTION

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Emerging Subspecialties in Neurology: Headache medicine

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Headache disorders affect half of the adult population and are considered one of the top 3 medical causes of disability worldwide.[1] There are over 300 different headache disorders. Hence, the diagnosis requires critical thinking.[2] Patients' symptoms often improve, so the treatment process is rewarding. While headache subspecialists have been studying the causes and potential treatments for a long time, substantial progress is now being made in the headache field. The headache field is emerging with the growth of academic headache centers and headache fellowship programs, new understanding of the pathophysiology of headache disorders, expanding therapeutic options, and the development of neurostimulation devices and immunotherapy. Headache fellowship programs started to be accredited in 2005 and have been rapidly increasing in number.[3] There are still not enough headache subspecialists to meet the national need and the majority of neurology residents are not exposed to the headache field while in residency.[3–5] We describe the history of the headache field, recent advances, and information about training and working in the headache field.

HISTORIC DEVELOPMENT

Classification. Nearly 2 millennia ago, Aretaeus of Cappadocia described 3 categories of headaches: (1) heterocrania (i.e., migraine), which he described to be mostly unilateral and associated with nausea, vomiting, photophobia, phonophobia, and olfactory changes; (2) cephalalgia (a milder headache); and (3) cephalae (a tension-type headache) (table).[6] In the 17th century, Thomas Willis identified some migraine etiologies: family history, diet, and season change.[6,7] He distinguished "intermitting" from "continual" megrim, recognizing that the intermitting megrim sometimes became continual.[6,7] Chronic paroxysmal hemicranias and cluster headaches were first described in the 18th century.[6] In 1981, the International Headache Society was formed to develop headache diagnostic criteria, advance clinical work, and promote research.[6]

Pathophysiology. In ancient Egypt and Greece, headaches were attributed to malevolent spirits.[6,7] The theory of humor imbalance followed.[6] Two new hypotheses emerged in the late 19th century: (1) Peter Wallwork Latham's vasomotor hypothesis stated that cerebral vasoconstriction caused aura and vasodilation caused headaches; (2) Edward Liveing's neurogenic hypothesis stated that migraine was a hereditary disease of the nervous system with nerve-storm paroxysms.[6] By the mid-20th century, John Hughlings Jackson thought of migraine as a "discharging lesion" originating by the "convolutions in connection with the thalamus opticus" with the headache being a postictal state.[6] At the time, Karl Lashley and Aristides Leao provided the first descriptions of cortical spreading depression (CSD).[6] The CSD leads to transient constriction and dilation of pial arteries, which introduce proinflammatory molecules in the environment and hence sensitize the peripheral trigeminovascular neurons.[8] Physiologic and emotional changes in homeostasis affect the hypothalamus, brainstem, limbic system, and cortex, which lead to a migraine prodrome or aura.[8] The hypothalamus activation leads to firing of preganglionic parasympathetic neurons in the superior salivary nucleus which both (1) stimulates neurotransmitter release from postganglionic parasympathetic neurons in the sphenopalatine ganglion, dilating the intracranial vessels and hence releasing proinflammatory molecules that activate the meningeal receptors, causing headache, and (2) activates trigeminovascular neurons in the spinal trigeminal nucleus.[8] Neuroimaging has shown that the pain processing pathway in the migraine brain is hyperexcitable and structurally different compared to the nonmigraine brain.[8,9]

Management. For the last 9,000 years, headache treatments have included trepanation, application of coca leaves to the incised skull, prayers, and head wraps in linen soaked with ailments such as vinegar and opium.[6,7] As a prelude to our modern Cefaly, a transcutaneous nerve stimulator, Galen applied electric torpedo fish to his patients' foreheads in the second century CE.[3] Headache management has become increasingly pharmacologic since the 17th century, when Culpeper started to prescribe valerian for nervous headaches.[7] In 1853, Romberg recommended lying in the recumbent position in a quiet dark room and drinking tepid tea to manage hemicranias.[3,6]

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Table Headache medicine throughout the ages[6,7,16,17]

Century	History
1st	Aretaeus described 3 categories of headaches: (1) a migraine type, (2) a tension type, and (3) a milder type
2nd	Galen applied electric torpedo fish to his patients' foreheads
17th	Willis distinguished episodic from chronic migraines and identified causes
19th	Primarily pharmacologic management of migraines with ergot (initially crude fungal extracts), cannabis, and coffee
Late 19th	Two main migraine pathophysiology hypotheses: (1) Latham's vasomotor hypothesis and (2) Liveing's neurogenic hypothesis
Mid 20th	First descriptions of cortical spreading depression
1943	Synthesis of abortive dihydroergotamine
1945	Opening of the Montefiore Headache Unit, the first headache center in the world
1948	First edition of Wolff's "Headache and Other Head Pains"
1954	Enrico Greppi opened the first headache center in Europe
1958	Synthesis of prophylactic UML-491 methysergide, a serotonin antagonist, and subsequent start of serotonin hypotheses
1960	IV serotonin found to help migraine headaches, but was not used clinically due to its side effects
1962	Creation of the American Headache Society
1970s	Invention of the CT scan
1979	First brain MRI
1981	Foundation of the International Headache Society
1988	First International Classification of Headache Disorders
1990	Synthesis of abortive sumatriptan
2005	United Council for Neurologic Subspecialties accrediting and credentialing of headache fellowships
2010	FDA approval of onabotulinumtoxinA injection for migraine prevention in adult chronic migraine patients
2013	International Classification of Headache Disorders 3 beta edition; *Headache* opened its Twitter account to help promote social awareness about headache research
2014	FDA approval of the first device for migraine prevention in adult chronic migraine patients, the Cefaly, a transcutaneous electrical nerve stimulator; FDA approval of SpringTMS, a single pulse transcranial magnetic stimulation, for treatment of acute migraine with aura
2015	A rat study identifies glucagon-like peptide-1 agonist as potential promising treatment for idiopathic intracranial hypertension
2016	Lasmitidan, a new 5-HT1F agonist, was proven efficient abortive of acute migraine in phase III trial SAMURAI; the phase III trial SPARTAN that includes patients with cardiovascular risk factors is scheduled to be completed in 2017; phase III trials of 4 CGRP monoclonal antibodies (LY2951742, ALD403, TEV-48125, and AMG334) for migraine prevention are scheduled to be completed by fall 2017

Abbreviation: FDA = Food and Drug Administration.

More recently, the main abortive options of the 19th century were ergot (initially in the form of crude fungal extracts until dihydroergotamine was synthesized in 1943), cannabis, and coffee.[6] The first migraine prophylactic agent was synthesized in 1958: methysergide.[6] In 1960, IV serotonin was found to help migraine headaches, but was not used clinically due to its significant side effects, which led to the search for a similar drug with less side effects.[6] Patrick Humphrey found it in 1990: GR43175, a selective antagonist to the B and D subtypes of the 5-HT_1 receptor, later renamed sumatriptan.[6]

CURRENT STATE OF THE FIELD

Diagnosis. While the majority of headache patients have primary headache disorders, headache specialists often manage patients with secondary headache disorders, including posttraumatic headache, idiopathic intracranial hypertension, giant cell arteritis, and other disorders.[10] Much time is spent on taking a thorough history to better differentiate the headache type.

Management. There is a wide range of evidence-based treatments. In the case of migraine, there are 7 different triptans, available in many forms ranging from tablets to sprinkles, nasal sprays, and injectables.[6] Lasmitidan, a selective 5-HT_{1F} receptor agonist, is being developed without vasoconstrictive side effects to hopefully abort migraine in patients with contraindications to triptans. The migraine preventive treatments include antiepileptic, antidepressant, and antihypertensive drugs, and onabotulinumtoxinA injection.[6] Calcitonin gene-related peptide targeted immunotherapy is being investigated as a promising migraine preventative therapy. There are also evidence-based behavioral treatments: cognitive behavioral therapy, progressive muscle relaxation therapy, and biofeedback. In addition, there are Food and Drug Administration–approved devices for migraine prevention using transcutaneous electrical nerve stimulation technology and for aborting migraine with aura using transmagnetic stimulation. Additional stimulators are under investigation. New procedures are being developed such as stereotactic injections directly into the sphenopalatine ganglion.

Future directions. Although there has been substantial progress in the understanding of the pathophysiology of migraines, cluster headaches, medication overuse headaches, and posttraumatic headaches, they are not fully understood. While hypotheses on the origin of migraines include the hypothalamus and the dorsal rostral pons, the driver of the migraine syndrome remains to be elucidated.[11] Furthermore, ongoing research on secondary headaches challenges our current understanding of headaches, e.g., how small pituitary adenomas are sometimes associated with severe headaches, and which neuropeptide secreted might affect the trigeminovascular system.[12] In addition, research questions remain on how to treat certain types of headache; e.g., there are few studies on when and how to manage posttraumatic headache.

FELLOWSHIP TRAINING

There are 33 United Council for Neurologic Subspecialties (UCNS)–accredited 1-year-long headache medicine fellowships, which accept from 1 to 3 fellows per year.[4] Many fellowship programs participate in the match process. The UCNS has developed curriculum requirements for the headache medicine fellowships,

Comment: Headache medicine as an emerging subspecialty—Irony and reality

In a narrative review, Begasse de Dhaem and Minen reframe headache medicine as an emerging subspecialty of neurology.[1] The authors provide a timeline spanning 2 millennia that chronicles historical, educational, scientific, diagnostic, and therapeutic developments in the field. Headache medicine as a discipline has existed for over half of a century, with organizational efforts long led by what is now known as the American Headache Society. The vast majority of headache specialists have been neurologists.

The authors note the acceleration of breakthroughs during the last decade, after a relative lull following the development of triptans. This era began with formal headache medicine fellowship credentialing, adding a level of legitimacy and visibility. Therapeutic developments have since been robust, including the approval of onabotulinumtoxinA and 2 noninvasive neurostimulation devices for migraine. The culmination of work in designer drugs for acute and preventive therapy has yielded exciting treatments including calcitonin gene-related peptide immunotherapies.

The evolution of the therapeutic landscape in headache medicine also includes clinic-based interventions such as peripheral nerve blocks. Procedural headache medicine has diversified clinical activity, helping to generate interest within neurology residency programs,[2] which may also attract trainees to the field. Headache medicine draws diverse expertise to the field, including concussion care, neuroimaging, neuro-ophthalmology, vascular and hospital neurology, women's health, orofacial pain, and behavioral medicine. Such clinical and scholarly collaboration adds to the interdisciplinary nature of the subspecialty.

The irony of the well-established field of headache medicine recast as an emerging subspecialty is grounded in reality: the current era has recently brought accelerating advances in organization, science, and translational and interdisciplinary therapies. Headache medicine provides an attractive, diverse career path for neurologists who are clinicians, scientists, educators, and advocates. It is of major public health importance to reduce the severe mismatch of headache specialists to the population that desperately needs them.[3]

1. Begasse de Dhaem O, Minen MT. Emerging subspecialties in neurology: headache medicine. Neurology 2017;88:e122–e125.
2. Robbins MS, Robertson CE, Ailani J, Levin M, Friedman DI, Dodick DW. Procedural headache medicine in neurology residency training: a survey of US program directors. Headache 2016;56:79–85.
3. Mauser ED, Rosen NL. So many migraines, so few subspecialists: analysis of the geographic location of United Council for Neurologic Subspecialties (UCNS) certified headache subspecialists compared to United States headache demographics. Headache 2014;54:1347–1357.

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including training in the basic science, diagnosis, and management of primary and secondary headache disorders in adults, children, and special populations (elderly, cardiac patients, pregnancy, lactating).[13] Fellows are prepared for the specifics skills required in day-to-day headache practice, such as (1) taking a thorough headache history, (2) differentiating primary from secondary headaches, (3) recognizing the patients who need brain imaging or inpatient admission, (4) long-standing care of complex patients with problems that require both multidisciplinary management (sometimes involving psychiatry, neuro-ophthalmology, neuroradiology, and vascular neurology) and combination of medications, behavioral treatment, procedures, and lifestyle modifications, (5) performing procedures, and (6) educating patients on lifestyle and behavioral management. The procedures performed in headache clinics include onabotulinum toxin injection, peripheral nerve block, and trigger point injection. Other options include neurostimulation and different infusions. In rare cases, patients with frequent, refractory, and severe headaches are admitted for inpatient headache care.

CAREER PROSPECTS There is a substantial shortage of headache specialists. There are no practicing headache subspecialists in 24 states.[3] Overall, the number of UCNS-certified headache subspecialists does not meet the needs of the migraine population.[4]

Headache medicine is a clinical field, but there are ample opportunities for research. A survey of American Headache Society (AHS) members at academic institutions showed that 72% worked mostly as clinicians, but specialists also spent time on research and teaching.[14] Some headache specialists also work for pharmacologic and device manufacturing companies.

At a time of concern about physician burnout, the future for headache medicine seems optimistic. In a survey of AHS members, 84.4% feel appreciated by their patients.[5] Most headache specialists stated that they did not regret their decision to go into headache medicine.[15]

Given the headache burden on society and the shortage of specialists, headache specialists are valuable members of health care. Now is an exciting time to enter the field given the recently exponential understanding of pathophysiology and development of varied treatment options (interdisciplinary, pharmacologic, behavioral, and procedural).

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REFERENCES

1. WHO. Headache Disorders [Internet]. WHO. Available at: who.int/mediacentre/factsheets/fs277/en/. Accessed October 31, 2016.
2. Evans RW. Diagnostic testing for the evaluation of headaches. Neurol Clin 1996;14:1–26.
3. Rizzoli P, Weizenbaum E, Loder T, Friedman D, Loder E. The evolution and geographic distribution of headache medicine fellowship programs and graduates: an observational study. Headache 2014;54:1591–1600.
4. Mauser ED, Rosen NL. So many migraines, so few subspecialists: analysis of the geographic location of United Council for Neurologic Subspecialties (UCNS) certified

headache subspecialists compared to United States headache demographics. Headache 2014;54:1347–1357.
5. Minen MT, Monteith T, Strauss LD, Starling A. New investigator, trainee task force survey on the recruitment and retention of headache specialists. Headache 2015;55:1092–1101.
6. Silberstein S, Lipton R, Dodick D. Wolff's Headache and Other Head Pains, 8th ed. New York: Oxford University Press; 2008:3–29.
7. Magiorkinis E, Diamantis A, Mitsikostas D-D, Androutsos G. Headaches in antiquity and during the early scientific era. J Neurol 2009;256:1215–1220.
8. Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. J Neurosci 2015;35:6619–6629.
9. Chong CD, Schwedt TJ, Dodick DW. Migraine: what imaging reveals. Curr Neurol Neurosci Rep 2016;16:64.
10. Ahmed F. Headache disorders: differentiating and managing the common subtypes. Br J Pain 2012;6:124–132.
11. Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. Brain J Neurol 2016;139:1987–1993.
12. Levy MJ. The association of pituitary tumors and headache. Curr Neurol Neurosci Rep 2011;11:164–170.
13. Certification: United Council for Neurologic Subspecialties [Internet]. Available at: ucns.org/go/subspecialty/headache/certification. Accessed November 8, 2016.
14. Finkel AG. Academic headache medicine in America: report of academic membership survey of the American Headache Society special interest section on academic affairs. Headache 2003;43:266–271.
15. Evans RW, Ghosh K. A survey of headache medicine specialists on career Satisfaction and burnout. Headache 2015;55:1448–1457.
16. Schuster NM, Rapoport AM. New strategies for the treatment and prevention of primary headache disorders. Nat Rev Neurol 2016;12:635–650.
17. Solomon S, Diamond S, Mathew N, Loder E. American Headache Through the Decades: 1950 to 2008. Headache 2008;48:671–677.

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