Headaches, Cluster and Otherwise: A Brief History

Headaches are one of mankind's oldest, most richly-documented diseases. The first description of headache comes by way of the Mesopotamians, in 4,000 B.C. The Mesopotamians, who occupied what is now modern-day Iraq, attributed the disease to "Tiu", an evil spirit who attacked his victims' heads [1]. Later, in 3,000 B.C., a Sumerian poet provided the first description of the "aura" associated with migraine:

The sick eyed says not 'I am sick eyed.'
The sick-headed (says) not, 'I am sick headed.'

The famous Greek physician Hippocrates later offered a more complete description of migraine with aura: *"Most of the time he seemed to see something shining before him like a light, usually in part of the right eye, at the end of a movement, a violent pain supervened in the right temple, then in all the head and neck... vomiting when it became possible, was able to divert the pain and render it more moderate."*
For Hippocrates, migraine was the result in the change of the "four humors": blood, phlegm, black bile and yellow bile. Yellow bile in particular, an excessive build-up thereof, was what he believed triggered a headache.

Aretaeus of Cappodocia, a Greco-Roman medical scholar writing in the first century AD, created the first recorded classification system for headaches [2]. Acute, short-lasting headaches he called "cephalalgia"; longer-lasting chronic headaches he called "cephalea"; and one-sided paroxysmal headaches he called "heterocrania". About cephalalgia sufferers (migraineurs) he wrote: *"They flee the light, the darkness soothes their disease; nor can they bear readily to look upon or hear anything disagreeable; their sense of smell is vitiated. Neither does anything agreeable to smell delight them, and they also have an aversion to fetid things; the patients, moreover, are weary of life, and wish to die..."*

A later Roman physician/scholar, Cladius Galen (A.D. 131 to 201), proposed that headache was the result of waste products acting on the brain. Disturbances in other areas of the body, he claimed, lead to the release of liquids or vapors that were harmful to the brain, causing headache. (This theory persisted until World War I when experiments conducted by the Germans in which soldiers were prohibited from defecating for several weeks failed to result in headache.) Galen is also credited with coining the term "hemicrania" to describe what is now known migraine. From hemicrania, the word became "hemicranium", then later "hemigranea", and then "migranea", "migrainea", and "migrana". The French then adapted "migrana" to "migraine" [1].

By the Middle Ages, migraine had become recognized as a discrete medical disorder. The treatments of this time were crude, involving hot irons, blood-letting, various herbal nostrums, even witchcraft [3]. However, mention of headache in literature became more common. In Shakespeare's *Romeo and Juliet,* Juliet's nurse suffers a headache, likely a migraine, on the eve of her mistress' wedding: "Lord how my head aches! What a head have I! It beats as it would fall in twenty pieces." Headache is also mentioned *Othello*, when the protagonist, Othello, complains to his wife, Desdemona: "I have a pain upon my forehead here."

In 1672, English doctor Thomas Willis devised another, more modern, classification system [2]. Headaches, in his view, were divided along the following parameters: 1. within or without the skull; 2. universal or particular; 3. short, continuous, or intermittent; 4, wandering or uncertain; 5. before, behind, or the side; and 6. occasional or habitual [4]. By this time, the condition of migraine had become relatively well known. Famous migraineurs include: Mary Queen of Scotland, Julius Caesar, John Calvin, George Bernard Shaw, Charles Darwin, Thomas Jefferson, Lewis Carroll, Mark Twain, Arthur Schopenhauer, Sigmund Freud, Anne Frank, John F. Kennedy, Vincent Van Gogh, and Elvis Presley [1, 5].

The first detailed description of cluster headaches appeared in 1641, courtesy of Dutch physician and anatomist, Nicolas Tulp [6]. Tulp described a patient who "in the beginning of summer season was afflicted with a very severe headache occurring and disappearing daily at fixed hours." The headache was said to rarely last "longer than 2 hours without any fever or generalized symptoms," and to reoccur "until the 14th day." Tulp also

noted that the patient "lost a great amount of fluid from the nose." This early description would fulfill all but one of the current International Headache Society's criteria for cluster headache.

Not until over a hundred years later, in 1745, would another Dutch physician, Gerhard van Sweiten, provide the first description of episodic cluster headache:

> *A healthy, robust man of middle age was, each day, at the same hour troubled by pain above the orbit of the left eye, where the nerve leaves through the bony frontal opening; after a short time the left eye began to redden and tears to flow; then he felt as if his eye was protruding from its orbit with so much pain that he became mad. After a few hours all this evil ceased and nothing in the eye appeared at all changed. I ordered blood to be let, gave antiphlogistic purgatives, I frequently applied cupping to the neck, vesicant adhesives, etc. but all in vain. But in order to understand this miraculous illness, I went to him at the time when he knew the pain would return, and I saw all the symptoms he remembered; in the carpal pulse however I found nothing changed. The patient reminded me, whilst I sat with him, that in the medial canthus of the eye he felt a large pulsation: I applied the apex of my little finger to the artery, which goes around the medial canthus of the eye, then with the other hand explored the carpal pulse; and thus I manifestly perceived how the artery in the canthus of the eye was pulsing more rapidly, and strongly than it naturally does. I therefore believed that there was a fever, but a tropical one; and I gave Peruvian bark and with luck cured it; and from this case I later learned to use similar remedies.*" [7].

The 1800s saw a series of papers written about syndromes that may or may not have been cluster headache. In 1822, British physician Benjamin Hutchinson, reviewing 28 case histories of patients with Tic Douloureux (a condition similar to cluster headache), noted that in many instances, the patients' pain was described as "periodical, recurring once in 24 hours; often remaining for several hours at a time, and then suddenly departing." Hutchinson suggested that these were instead cases of "hemicrania"; later researchers speculated that he had in fact stumbled upon some of the earliest descriptions of cluster headaches, notwithstanding the scant evidence afforded them [8]. University of Berlin Professor Moritz Heinric Romberg, in his 1840 book, *A Manual of Nervous Diseases of Man*, described a cluster headache-like condition known as "Ciliary Neuralgia":

> *Painful sensations in the eye, which are generally confined to one side, and are excited or increased by rays of light and by visual efforts, are the characteristic symptoms of this affection. In the higher degrees photophobia is present; this is therefore the term generally applied to the affection. The patient avoids solar and artificial light, as the bulb of the eye becomes painful when exposed to their influence, and the eyelids contract painfully. The pupil is contracted. The pain not unfrequently* [sic] *extends over the head and face. The eye generally weeps and becomes red. These symptoms occur in paroxysm, of a uniform or irregular character, and isolated or combined with facial neuralgia and hemicrania."* [Ibid]

In 1878, Albert Eulenburg, Professor of Neurology at the University of Greifswold, described painful headache-like attacks that were accompanied with tearing, eye-redness, constricted pupil, and drooping eyelid--classic cluster headache autonomic symptoms. These attacks, which he called "hemicrania angioparalytica" or "neuroparalytica", lasted anywhere from a few hours to half a day, with "alternating remissions and exacerbations." The fact that they lasted so long, however, suggests something called "hemicrania continua", a close cluster headache relative [Ibid].

R. Bing in 1912 wrote of a disease that included a burning sensation in the face, autonomic features, and a recurring pattern, calling it erythroprosopalgia. (Erythro (red) + prosopon (face) + algia (pain)). And in 1925, French physicians Vallery-Radot and Blamontier described a 38-year old female with severe, recurrent right-sided headache with lacrimation (tearing) and rhinorrhea (runny nose). Neither of these, however, could be conclusively deemed cluster headache due to insufficient evidence [Ibid].

But in 1926, London neurologist Wilfred Harris did provide such a conclusive description, in fact several

of them. In one account, he describes *"A young man of 25, when aged 19 began to suffer from daily attacks, for three or four weeks every year, of severe pain in the back of the right eyeball and forehead, with lachrymation* [sic] *and reddening of the eye; this would last for an hour or two, no nausea, but voracious appetite accompanying the neuralgia. During the last two years he had had similar attacks of pain behind the left eyeball, and they would then transfer and become severe on the right side.*" [9]. This account is the first to meet the current International Headache Society's criteria for cluster headache, including recurrent pattern, autonomic symptoms, and pain around/behind the eye. In another account, Harris writes: *"A man, age 47, had his first attack of neuralgia in January 1917, when in the trenches in front of Beaumont Hamel. The pain struck him suddenly across the left temple and forehead, and lasted for three-quarters of an hour, like an 'electric battery', while his face became flushed and he felt faint. The neuralgia recurred thrice daily, at about eight hour intervals for six weeks, and then disappeared entirely for two years...."* Harris first called these cases "periodic migrainous neuralgia" and then later "ciliary neuralgia." He is now widely-regarded as providing the first full-length description of cluster headache.

The first American physician to report on cluster headaches was Walter Dandy of Johns Hopkins. In 1931, Dandy described a 50-year old man who since the age of 17 had experienced recurrent pain-attacks in the eye and the upper jaw area. These attacks, lasting around 30 minutes each and occurring up to 6 times daily, were accompanied by drooping eyelid, facial sweating, runny nose, and slowed heart rate. Dandy himself, however, was unaware that these were cluster headache, and instead called them migraine [8].

It was another American neurologist, Bayard Taylor Horton, who would be the first to propose a theory of pathogenesis for cluster headache. Horton attributed the disorder to a unique form of histamine sensitivity, and used histaminic desensitization therapy to treat a number of refractory patients [10]. In a 1939 paper, he writes, *"Our patients were disabled by the disorder and suffered from bouts of pain from two to twenty times a week. They had found no relief from the usual methods of treatment. Their pain was so severe that several of them had to be constantly watched for fear of suicide. Most of them were willing to submit to any operation which might bring relief."* [11]. It was from this paper that the disease's nickname, "Suicide Headaches", was coined. Horton called this condition alternately "erythromelalgia of the head", "histaminic cephalgia" or simply, "cephalalgia." Later researchers would call it "Horton's headache" or "Horton's Syndrome" in his honor. Along with his associates MacLean and Craig, Horton was the first to point out that attacks can be triggered by alcoholic beverages [8].

Dr. Charles Kunkle, writing with Pfeiffer, Wilholt, and Hamrick for the North Carolina Medical Journal in 1954, was the first to use the term "cluster headaches." A few years later, Drs Friedman and Mikropoulos from the Headache Unit of the Montefiore Hospital in New York published an article in the journal Neurology called "Cluster Headaches", after which the term was accepted by the AD HOC Committee on Classification of Headache [Ibid]. Dr. Kunkle was also one of the first to point out the periodicity of cluster headaches, their tendency to occur in regular, metronomic "clusters" [6].

Kunkle, along with Swedish neurologist Karl-Axel Ekbom, Lee Kudrow, Ninan Mathew, Ottar Sjaastad and others, are the pioneers of the early modern cluster headache research period. Ekbom was the first to employ lithium to treat the disease [12]. He was also the first to distinguish between episodic and chronic cluster headache, and the latter from chronic cluster headache unremitting from outset and chronic cluster headache that evolves from episodic [13]. Kudrow, Mathew, Sjaastad and others made similar contributions by advancing research ideas, conducting studies, and authoring papers and books [14].

Today, thanks to the introduction of headache journals, national and international headache societies, headache symposiums, citizen advocacy and support groups, as well as advances in imaging and testing technologies, there is a deep body of headache-related knowledge to draw from. We've come a long way from the days of invoking "evil spirits" or the "four humors" to explain headache pathology. And yet, as a distinct medical condition, cluster headache remains largely misunderstood, in some cases even by neurologists themselves. As I will show in subsequent chapters, cluster headache is often misdiagnosed and mistreated. For instance, many primary physicians and neurologists are ignorant of the benefits of oxygen therapy, notwithstanding the International Headache Society's recommendation that it be used as an abortive treatment [15]. There is also enormous resistance to alternative therapies such as LSD and psilocybin, therapies

that have shown unparalleled prophylactic potential. If it is true that the ultimate purpose of medical research is the alleviation or mitigation of pain, the future of cluster headache research must be one that challenges cultural and bureaucratic stigmas. It must be one that takes an "all-of-the-above" approach, looking outside of the box, embracing alternatives, resisting the imperatives of Big Pharma. It must labor not only in the service of increasing the knowledge-base of cluster headaches, but in also in raising awareness about a disease that is far too often overlooked and underappreciated.

References

1. Diamond S. Franklin MA. *Headache Through the Ages*. New York: Professional Communications Inc. 2005. Print

2. https://en.wikipedia.org/wiki/Headache#History

3. https://www.atrainceu.com/course-module/1473434-79_migraine-headaches-module-01

4. Martelletti P, Steiner TJ. *Handbook of Headache: Practical Management*. New York: Springer. 2011. Print

5. http://www.healthcentral.com/migraine/migraineurs.html

6. Gordon N. History of Cluster Headache. *Current Pain and Headache Reports* 2004, 9:132-134

7. Pearce, John MS. *Fragments of Neurological History* London: Imperial College Press. 2003. Print. 176- 178

8. Mathew NT. *Cluster Headache.* Jamaica: Spectrum, 1984. Print]

9. Boes CJ, Capobianco DJ, Matharu MS, Goadsby PJ. Wilfred Harris' early description of cluster headache. *Cephalalgia* 2002; 22:320-326. London.

10. Fanciullacci M. When cluster headache was called histaminic cephalalgia (Horton's headache). *J Headache Pain* (2006) 7:231-234

11. Fletcher J. A General Description Of Cluster Headache Disorder. Journal of Neurology & Stroke. Volume 4 Issue 1 - 2016

12. Abdel-Maksoud MB, Nasr, A, Abdul-Aziz A. Lithium treatment in cluster headache: review of literature. European Journal of Psychiatry 23(1): March 2009.

13. Ekbom K. Evaluation of clinical criteria for cluster headache with special reference to the classification of the International Headache Society. *Cephalalgia.* 1990; 10:195-7

14. Ekbom K, Waldenlind E. Cluster headache: the history of the Cluster Club and a review of recent clinical research. *Functional Neurology* 2004; 19(2): 73-81

15. Diagnosis, symptomatic therapy and preventive therapy of cluster headache. *J Headache Pain* (2001) 2:168-179