Bedside to bench and back

Challenging Conventional Wisdom, Migraine

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Definition

Migraines are recurrent headaches separated by symptom-free intervals and accompanied by nausea and light sensitivity. Migraines are often accompanied by visual symptoms and are relieved by sleep; furthermore there is usually a throbbing quality. More often than not there is a family history of migraine.

Migraines are important.

About 13% of the population get migraines, at least occasionally (Stewart, Shechter et al. 1994). Women are especially likely to have migraine (3:1 female:male ratio, 4:1 during childbearing years). Women between 30 and 45 experience the peak prevalence, roughly 25%. Women get more migraine than men because of hormonal fluctuations, and migraines abate in women in menopause. About 4% of children have migraines.

Migraines cause considerable amounts of dizziness

Table 1: Patients with Migraine having Vertigo

Percent of migraine patients with vertigo	Comment	Authors
26.5 %	Unsolicited migraine (n=200)	(Kayan and Hood 1984)
33 %		(Selby and Lance 1960)
42 %	Migraine with aura	(Kuritzky, Ziegler et al. 1981)

In practices focused on treating migraine, 27-42 % of patients report episodic vertigo (See table 1). A large number (about 36%) of these patients experienced vertigo during headache-free periods. The remainder experience vertigo either just before or during the headache. The incidence of vertigo during the headache period is higher in patients with aura as opposed to in those without aura.

In practices focused on treating vertigo, 16-32% of patients have migraine (Savundra et al, 1997). The prevalence of migraine in the general population is 13% (Stewart et al, 1994), so from table 1, one would predict that between 3 and 5% of the entire population would have migraine associated vertigo. The prevalence of migraine with vertigo in Germany was recently reported to be only 1% (Neuhauser, Radtke et al. 2006). This seems a bit low from these rough calculations, but nevertheless one can conclude that there is an immense amount of migrainous vertigo, and that migrainous vertigo is an extremely common cause of vertigo in the general population. The prevalence of Migraine associated vertigo is certainly far higher than that of Meniere's disease, which occurs in only 0.2% of the US population (Wladislavosky-Waserman et al, 1984).

New data from the bench

Conventionally, and especially about 25 years ago, migraine was felt to be related to vasospasm -- blood vessels went into spasm, causing the aura, and then there was a hyperemia associated with a headache. Associated with this train of thought were observations that vasodilation can trigger migraine, and vasoconstriction abort it. Later it was suggested that electrical changes in the brain (spreading depression) was the underlying mechanism for neurological abnormalities (aura) associated with migraine, although this did not explain the occasional strokes and the far more common cerebellar white matter damage observed in the MRI of persons migraine (Kruit, Launer et al. 2005). Recently it has been suggested that serotonin neurotransmitter abnormalities underpin migraine, based on the observation that serotonin drugs such as the triptans are very effective medications for pain as well as for associated symptoms.

Research has also documented a greatly increased sensitivity in migraine sufferers to many sensory inputs. (Goadsby 2001; Goadsby 2005). Light (photophobia), sound (sonophobia), smells (osmophobia), and motion sensitivity are highly prevalent in persons with migraine headache. Another similar sensory abnormalities is allodynia (cutaneous hypersensitivity). Motion sensitivity often begins in childhood, prior to significant headache(Bille 1962). Sensitivity to various sensory inputs can be detected even in persons not having headaches. Persons with migraine have recently been shown to have thicker sensory cortex than non-migraineous persons(DaSilva, Granziera et al. 2007). These observations suggest early onset "wiring" differences in persons with migraine.

Review of current neuroanatomy and neurochemistry

Head pain in migraine is largely **generated** from irritated or irritable intracranial blood vessels. Pain impulses are transmitted primarily through the trigeminal nerve, but also via the glossopharyngeal and vagus cranial nerves. These signals are proceed in the principal trigeminal sensory nucleus, and then ascend to the thalamus.

Pain is **inhibited** by descending signals from the frontal cortex going to the hypothalamus and periaqueductal gray (PAG). The PAG then goes to the rostral ventromedial nucleus (RVM) which ultimately projects to the medullary and spinal dorsal horns. The PAG-RVM system contains serotonergic (5-HT) excitatory neurons that inhibit transmission from the spinal trigeminal nucleus.

Review of pathophysiology

Migraine may be initiated by cortical spreading depression (CSD). This is a suppression of electrical activity in the brain, followed by oligemia. The evidence for CSD is strongest for persons who have migraine with aura. CSD causes release of various neurochemicals including NO. This is followed by neurogenic inflammation of blood vessels and pain.

Underlying the CSD may be differences in cortical wiring. Thicker sensory cortex is found in migraine patients (DaSilva, Granziera et al. 2007). Furthermore, persons with migraine have "hyperexcitable cortex" (Aurora, Ahmad et al. 1998; Aurora and Welch 2000). These findings may be associated with reduced thresholds for sensory input and expansion of neuronal receptive fields (i.e. photosensitivity, phonosensitivity, etc).

Considering this background (See Ramadan for more details (Ramadan 2005)), at the present writing, in 2008, all of our old ideas are still viable, but we now can understand why certain treatment approaches work by using our knowledge of the neurobiology.

Back to the bedside -- TREATMENT

There has been gigantic changes in the treatment for migraine in the last decade.

Abortive medications:

Table 2: Abortive medications for migraine

Onset	Medication	Dose
Rapid	Sumatriptan (Immitrex) injection	6 mg
	Sumatriptan tablet	100 mg
	Eletriptan (Relpax) tablet	40 mg
	Rizatriptan (Maxalt) sublingual	10 mg MLT
Medium	Zolmitripan (zomig)	5 mg
	Naratriptan (Amerge)	1mg, 2.5 mg
Slow	Frovatriptan (FROVA)	2.5 mg to 7.5 mg/24 hours

Migraine treatment was enormously impacted by the advent of use of triptans (see table 2). Triptans are 5-HT1B agonists, that act to suppress transmission of pain impulses at the trigeminal nucleus. Suddenly it was possible to offer the option of taking a medication that often provided complete relief of headache within about 30 minutes.

While wonderful advances for migraine pain, triptans are impractical drugs for dizziness. Their "reactive" nature -- one takes them after the headache or dizziness begins -- makes them nearly useless for people who cannot afford to become suddenly dizzy while driving down the road. For this reason, people with significant migraine and dizziness nearly always need to use a migraine prevention medication.

Migraine prevention drugs

Table 3: Medications that are usually effective in preventing migraine

Family	Medication	Starting dose	Maximum	Common Side Effects

			Dose	
Anticonvulsant	Topiramate	25 mg BID	100 BID	Tingling in extremities Weight loss Word finding difficulty High cost (not generic)
	Sodium valproate	250 mg	1000	Tremor (common) Weight gain
Antidepressant	venlafaxine	12.5 mg	37.5 BID	Sexual dysfunction (rare)
	amitriptyline	10	50	Weight gain (common) Lethargy
Antihypertensive	verapamil	120 mg SR	240 SR BID	Constipation (common)
	propranolol	60 mg LA	180 LA	Fatigue (common) Sexual dysfunction (common)

Otolaryngologists frequently are told to prescribe amitriptyline and/or nortriptyline for migraine prophylaxis. These inexpensive generic drugs are effective prevention medications, but often their use is associated with very significant side effects. Weight gain is the most troublesome. It is often difficult to convince a woman of childbearing age to take a medication that could make her gain 25 lbs and make her sleep an extra hour or two every day. Fortunately, there is presently a much larger repertoire of migraine prophylaxis drugs than these older agents.

For those who don't benefit sufficiently from or refuse lifestyle modifications (stop eating chocolate ?) , and have more than 2 severe headaches/month, a daily medication as outlined in table 3 may be worthwhile. These are generally effective in about 75% of those who take them for 1 month, but they do require daily regular use. In general, migraine patients are often medication sensitive as well as have sensitive stomachs (and eyes, ears, etc), and lower doses of medication may be necessary than is advised in popular manuals such as the PDR.

These drugs fall into three major classes: anticonvulsants, antidepressants, and antihypertensives. For brevity, only one or two representatives of each class is included in table 3.

Topiramate (Topamax) -- is an excellent prevention medication. It has largely replaced sodium valproate, which was the only approved prevention medication in 2001 (Mathew 2001). Side effects of Topamax are generally minor and include weight loss (not necessarily a bad thing), tingling in the extremities, and word finding problems in roughly 10%. The mechanism of action of the anticonvulsants is likely related to prevention of CSD.

L- Calcium channel blockers (verapamil 120 SR) are also excellent migraine prophylactic medications. There are no cognitive side effects, but constipation, peripheral edema and minor decreases in blood pressure are common. The mechanism of action of the calcium channel blockers is not very clear, but may relate to effect on blood vessels or release of CGRP (Akerman, Williamson et al. 2003).

Beta-blockers such as propranolol are also effective migraine prevention agents, but they also lower blood pressure as well as have some untoward sexual side effects. It is not necessary for beta-blockers to cross into the CNS, and their mechanism of action may lie outside the brain.

Venlafaxine (Effexor), is an antidepressant that is a very effective migraine prophylactic in very low doses(Bulut, Berilgen et al. 2004). It is a dual 5-HT and NE reuptake inhibitor. The mechanism of effect in migraine is unclear as clean "SSRI" drugs are relatively ineffective. Practically however, this drug seems to be very useful in managing the sensory amplifications seen in migraine. Side effects for the tiny doses used for migraine (about 37.5 mg QAM) are negligible.

In conclusion:

Migraine is a common condition that is important to the otology community because it accounts for a large number of vertigo cases, especially compared to less prevalent inner ear disorders such as Meniere's disease. There have been numerous major improvements in medication treatment of migraine in the last decade. There have recently been major advances in our basic understanding, but we still have far to go.

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