Curr Pain Headache Rep (2013) 17:366
DOI 10.1007/s11916-013-0366-3

MIGRAINE (R COWAN, SECTION EDITOR)

Why Do Migraines Often Decrease As We Age?

Frederick G. Freitag

Published online: 1 September 2013

Abstract Migraine undergoes both an evolving state in the formative years but also has a remitting state which bears resemblance to the former. Underlying genetics may contribute to the initiating sequence for these processes but the patient's lifetime environment may influence the expression of the disease. Systems rarely thought of in terms of neurologic disease such as the inflammatory system may have significant contributions to modulating this process and accounting for the clinical presentation of migraine.

Keywords White Matter Hyperintensities · Vasodilatory Capacitance · Endothelium · Microglia · Immunocompetent · Spreading Depression · Neurogenic Inflammation · Oxidative Stress · Ferritin

Introduction

Sometimes it is said about the elderly, part in derision, and part in jest that they are "entering their second childhood". To a degree this is something that we might say about migraine in this setting. Just as there are few children who have migraine before the age of 5 years, there are also not many patients who have migraine in their eighth decade of life. We know little enough about the how and why migraine even begins, so what do we know of the demise of migraine?

Epidemiology

Migraine is estimated to affect nearly 15 % of the population. [1•] In the United States, about 6 % of men and 18 % of women experience at least one migraine in a given year. The lifetime risk of migraine is about 18 % and 43 %, respectively [2]. In Europe the rates are slightly lower [3] and even lower in Asia and Africa than in Western countries [4]. Chronic migraines occur in approximately 1.4 to 2.2 % of the population [5].

Migraine is more common in boys than in girls before adolescence. With the rise in the sex steroid hormones and the entering of puberty, prevalence of migraine increases more rapidly in girls than in boys. This increasing prevalence of migraine continues from late childhood, through the early years, until the approximate age of 40 years, after which migraine prevalence begins to decline [6]. After about age 50 years the prevalence of migraine rapidly declines such that by age 70 years the prevalence of migraine approximates that of the middle teen years [7]. While migraine itself tends to decline with age, the transformation of migraine to a higher frequency disorder progresses steadily through the adult years such that by age 70 years or greater the occurrence of migraine 10 or more days per month is nearly double that seen during the decade of the 40s [8].

There are a variety of co-morbidities which have been associated with migraine [9]. Of note there is an increase in the occurrence of depression with age along with an increase in the number of days per month with migraine. While cerebrovascular disease is a well-known entity with advancing years and has been linked with migraine, those most likely to be affected are those who are relatively younger and with a history of migraine aura. White matter hyperintensities (WMH) are reported related to migraine and may represent subclinical infarcts, though these findings tend to be relegated to the cerebellum, and again in those with migraine aura as compared to that seen with migraine without aura as will be discussed later. The etiology of these changes related to cerebrovascular disease was studied by Meyer and colleagues [10]. They found that the controls and those with continuing severe migraine had a decline cerebral capacitance. Those with a history of migraine which had abated or remitted or where they experienced migraine aura without the headache had a more significant decrease in this parameter. They hypothesized based on their study that this diminished cerebral vasodilator capacitance as part of aging was due to atherosclerotic changes which were made worse by risk factors for

This article is part of the Topical Collection on *Migraine*

F. G. Freitag (✉)
Department of Neurology, Medical College of Wisconsin, 9200 W. Wisconsin Ave, Milwaukee, WI 53226, USA
e-mail: dhcdoc@gmail.com

stroke, including TIAs, lacunar infarctions and menopause. Similar findings were reported by the group from Henry Ford [11].

Changes in Headache Characteristics in Later Life

It is an interesting change that, over the years, less people are afflicted with migraine episodes but those who do experience them appear to be at risk for a higher percentage of their days being afflicted with the attacks. Beyond this, how else does migraine change over the years into later life?

A study from Japan found that migraine with aura occurred in a 6.3 % of their study population with a peak prevalence in the fifth decade. Typical migraine aura without headache occurred approximately half as often (3.2 %) and tended to occur more commonly in a slightly younger group than those with headache following their aura or later in life after the age of 60 years [12]. Kelman [13] reported on 952 patients with migraine and found that 38 % of females and 33 % of males had experienced attacks of migraine with aura. Of these, 33.5 % had experienced migraine aura without headache; the age related time course of this was not reported.

Few studies have been undertaken to assess changes in the clinical spectrum of migraine over the adult years, as compared to the differences that exist in migraine in children and adolescents compared to adults with migraine which played a significant role in the changes to the International Headache Classification (IHC) criteria [14]. By the same token we also know little of the impact of age related change on migraine treatment issues, especially for the elderly with migraine, an area essentially unstudied.

Probable migraine, defined loosely as migraine lacking one of the IHC criteria for migraine, was examined in the American Migraine Prevalence and Prevention (AMPP) study [15] which found a 1 year prevalence of this in 3.9 % of males and 5.1 % of females for an overall prevalence of 4.5 %. They examined the prevalence of this variant of migraine over the course of the decades of life. It was highest in the fifth decade for men with a prevalence of 6.5 % compared to women where the peak prevalence was in the ages 30 through 39 years with a 6.7 % 1 year prevalence rate. It declined in those over age 69 years where the one year prevalence rate was 2.7 % for men and 3.7 % for women.

As with migraine with aura where the prevalence changes with age, so in probable migraine there is suggestion that with age migraine with or without aura may transform to probable migraine [16]. Whereas those over age 70 years with probable migraine gave a past history of having typical migraine earlier in life or had resolution of their migraines after the age of 60 years.

Just as migraine in children resembles migraine in adults with selected differences, so does migraine in the later half of life demonstrate differences from migraine during the periods of peak prevalence. The characteristic unilateral nature of migraine was found to occur in only 38 % of older migraine patients compared to 57 % of those in the prime adult years. They also found reduced prevalence of nausea, vomiting, and photophobia and phonophobia in the elder migraine population, all of which were statistically significant. On the other hand, migraine premonitory symptoms occurred more commonly in the elderly than in the younger adult population [17].

Another study, conducted as a follow-up to the above used a telephone interview process [18••]. This showed a decline with aging in characteristics of the pain of migraine such as throbbing, unilaterality, severity and exertional exacerbation. Similarly, nausea, photo- and phonophobia also tended to decline with advancing age. On the other hand, as had been seen as well, the occurrence of aura increased with increasing years of life.

A different set of outcomes, however, came from a study from Vienna where they examined 260 consecutive patients with migraine ranging from adolescence onward [19]. As typical in many migraine studies, women outnumbered men nearly 2 to 1 and were in general older than their male counterparts. In their study, rather than examining a steady continuity of age or even a decades approach to assessment as others have done, Wöber-Bingöl et al examined a young age range then two rather broad age ranges in which historically the prevalence of migraine tends to overlap which may have a confounding effect on their data. That said, they found that men with increasing age tended to have more frequent headaches at each of the age ranges (under age 14 years, 15-40 years and over age 40 years) but not so in women. On the other hand, women trended towards more attacks per week as well as longer duration of migraine. The prevalence of unilateral pulsatile pain increased as did exacerbation of pain with activity in women with increasing age. These changes were not seen in men with advancing age. Migraine associated symptoms were not related to age in men and only phonophobia increased with age in women. As compared to other studies where aura increased with age, they found that aura peaked in the 15 to 40 years age range and was diminished in the younger and older spectrum of patients. They found no sex related differences in the occurrence of aura.

What Do We Know about How the "Healthy" and Migraine Brain Changes with Age?

While there is no small amount of research being done examining the changes in the brain associated with neurodegenerative disorders such as Alzheimer's Disease, or on disorders with serious public health consequences such as stroke to attempt to understand the mechanism by which migraine "goes away", so examination of age related changes associated with migraine as

well as unrelated to significant disease would seem to be appropriate as there appears to be no "serious" long term sequela to migraine.

WMH are not unique to the migraine population. A large multicenter, multinational study, the leukoaraiosis and disability (LADIS) study, examined WMH in relationship to a variety of epidemiologic and risk factors [20]. The LADIS project studied the role of WMH as an independent predictor of the transition to disability in initially non-disabled elderly. In this study, 639 elderly subjects who were minimally impacted by neurologic disease were enrolled. They had undergone MRI and had WMH as an incidental finding. The WMH were seen on T-2 images and those that were not associated with a bright FLAIR signal were considered normal-appearing WMH (NAWM). Longitudinal evidence suggests that the periventricular WMH appear earlier and increase in volume at a faster rate than subcortical WMH. These observations suggest that there may be pathologic differences between periventricular and subcortical WMH. The study showed a pattern of significant associations with age and hypertension, and to a lesser degree with male gender and smoking. The anatomic distribution of these lesions found them most commonly in the area around the anterior horns of the lateral ventricles, then along the lateral borders of the ventricles. WMH were also seen with high probabilities in the deep white matter region more laterally, extending towards the precentral gyrus. Migraine with aura was more commonly associated with WMH than those without aura, but there was no correlation with the location of the WMH and the sidedness of the headache or the aura [21]. WMH tend to be seen somewhat more commonly with increasing age. WMH more commonly are found in the lateral deep white matter and around the centrum ovale. There occurrence is distinct from other associated risk factors for WMH and were less likely to be associated with FLAIR.

With improved diagnostic tools the frequency of dying patients being sent for post mortem examination has declined. The advent of use of the MRI has helped to contribute to this. Unfortunately this has also provided an information gap regarding the nature of WMH. A recent study attempted to address this, though the sampling selection was small, by examining post mortem samples and correlating findings with MRI [22]. These patients resembled neurologically those in the previous study. They found that the WMH at the angle of the ventricle showed a visibly discrete boundary, coinciding with area of a hyperintense signal on the FLAIR in the frontal, temporal, and occipital lobes only. They also found dilated perivascular spaces in the periventricular WMH. This contrasted with a relatively normal appearance of the tissues associated with subcortical WMH where the signals from the WMH were more diffuse. Detailed examination of WMH associated with FLAIR demonstrated a loss of myelin basic protein immunoreactivity compared with NAWM. Similarly axonal density shown with phosphorylated neurofilament immunohistochemistry, was decreased to a greater extent in the periventricular WMH than subcortical WMH. These results suggest that the NAWM may have fundamentally different etiological causation. In patients with migraine these WMH again differentiate themselves from those seen associated with other causes of WMH in that they are found to correlate with the presence of elevated antineuronal antibodies [23••] but without other autoimmune markers.

There are also changes in the gray matter (GM) with normal aging characterized on MRI studies [24] and on microscopic examination these GM volume losses appear to result from neuronal dendritic arbor shrinkage and synaptic losses. In migraine patients the use of a 3-T MRI scanner was used to examine the GM changes [25]. They found that migraine patients had areas of reduced GM density in the frontal and temporal lobes but increased periaqueductal GM (PAG) density. In those with migraine with aura they had a further increase in density of the PAG and of the dorsolateral pons. There was a strong correlation between reduced GM density and increasing age and longer disease duration.

While we have moved away from a vascular basis of migraine, the role of the blood vessels in migraine remains an important part of the pathophysiological basis of the current theories of migraine. The endothelium has been postulated to be involved in this process accounting for the leakage of fluids in the perivascular space [26, 27] as part of sterile inflammation that Wolff described and which may be the same as the neurogenic inflammation which we associate with migraine and which is associated with autoimmune antibodies as described above. The endothelium is important in the regulation of the vasodilatory and vasoconstrictive properties of cerebral vessels [28] and may play a role in the loss of the vasodilatory response with age and with changes in migraine occurrence as previously noted. This regulation of the smooth muscle cells occur via nitric oxide linked cGMP and via prostacyclin modulation of cAMP, both of which result in vasodilation with an intact endothelium. Denuding of the endothelium which may be associated with plaque production and disruption of an intact endothelium allows for vasoconstriction to occur with stimuli. While this would be unusual, the lifespan of endothelial cells has been estimated to be on the order of 30 years and regenerated or replacement endothelial cells appear to lose or have mitigated their ability to either protect against vasoconstriction or promote vasodilation.

The glial cells were thought to be inconsequential in brain disorders; however, in the past few years there has been increasing interest in these cells and their functional roles. Bartley [29] proposed that glial cells could play a role in migraine pathogenesis via their link to inflammatory processes and release of a variety of inflammatory modulating chemicals. One of these is in modulating the inflammatory response in neural tissues along with a variety of inflammatory modulators including immune system cells, and has taken on increasing

interest in degenerative disorders and also in a variety of other disorders not typically associated with inflammation including depression and migraine. It has been postulated that early developmental challenges to the system may underlie the expression of this system [30]. Neuroinflammation may result from chronic glial activation involving both microglia and astrocytes and an exaggerated expression of proinflammatory mediators within the brain such as cytokines. Still to be elucidated is whether the inflammatory response is the cause or effect of neuronal dysfunction. It has been proposed [30] that infectious disease processes in development lead to a prolonged sensitization of glial cells which when challenged later in life mount an inflammatory response which may impact on neuronal health and disease. The mechanisms remain poorly understood and evidence has demonstrated both changes supportive of cell health and also of cell degeneration.

Cytokines have been implicated in the mechanisms responsible for impairment associated with pathology and also in improving synaptic plasticity mechanisms. Tumor necrosis factor (TNF)-α is important for activity-dependent synaptic production within the hippocampus. TNFα, interleukins [IL] and prostaglandins can impact cognitive function. This can be both detrimental when there is an overexpression of the IL-1 receptor antagonist and also necessary for optimal hippocampal function. CD4+ T cells may specifically recognize CNS self-antigens such as those associated with WMH in migraine, and play a role in neurogenesis via interactions with meningeal myeloid cells and the production of IL-4.

Microglia are the primary immunocompetent cells of the brain. Astrocytes are the largest glial cell population within the brain with an established role in synaptic plasticity mechanisms. There is increasing evidence for a role for microglia in normal synaptic plasticity mechanisms within the adult brain. Microglia are dynamic, even in the resting state and survey their environment by extending and contracting processes into nearby synapses in activity dependent frequencies especially following visual stimulation. This movement of microglial branches has been demonstrated to occur [31] in relationship to spreading depression. While the cortical cells are active the microglial branches move little; however, with the advent of spreading depression increasing activity of these synaptic branches increases until abrogated by cessation of the spreading depression. Spreading depression [32] has a negative impact on microglial cell health through increased oxidative stress and production of TNFα which enhances spreading depression by the microglia. Microglia [33•], with increasing age, become dystrophic in appearance. This is represented by slight enlargement of the cells with a loss of fine branches and the formation of cytoplasmic materials. These changes are widespread but may be more commonly seen in areas of disease. Along with these dystrophic changes there are also elevated levels of ferritin. Increasing amounts of iron deposition are seen in the PAG in patients with migraine where there is a correlation between frequency of attacks and years with migraine and the deposition of iron [34]. This iron deposition leads to damage through oxidation of iron release of the superoxide, which may contribute oxidative stress related. Mitochondrial DNA (mtDNA) is highly susceptible to damage from reactive oxygen species because of their relative lack of protective histones which may contribute to mtDNA mutations further exacerbating the dysfunction and inhibiting their critical role in the autophagic process that removes damaged organelles.

Spreading depression has been linked to the microglia and their inflammatory modulating chemicals. A study [35] examining spreading depression to activate pain pathways of the trigeminal nucleus failed to find a role for neuroinflammatory pathways to play a role in the genesis of migraine. They demonstrated a lack of increase in CGRP or PGE2 associated with spreading depression which is analogous to the findings for these chemical during the migraine aura. Further contributing to the disconnect between spreading depression and migraine pathogenesis was the failure of tonabersat [36] to prove effective in migraine treatment.

Fundamental to neuronal communication are neurotransmitters, a number of which have been linked to a variety of disorders. Though the data is comparatively old, [37] demonstrated that there was not only reasonable similarity between monkey and human brain changes in neurotransmitters but that there was a paucity of changes occurring in most of the brain with a variety of neurotransmitters. Of interest though were the findings from the putamen, though not typically linked to migraine, which showed that monoamine neurotransmitters, such as serotonin and norepinephrine, were at their lowest levels in the very young monkey then peaked in the second decade only to decline gradually thereafter. While there was no age related increase in serotonin receptors in the visual cortex, there was an age related decline in serotonin along with an age related increase in glutamate receptors in healthy monkeys. More recent studies use PET scanning have partially verified these results; however, they have continued to leave a variety of questions unresolved as to whether the nature of these changes are directly related to changes in serotonin, pre- and post-synaptic receptors, and intracellular metabolism as causative of the changes with many of the serotonin receptors, such as the 5HT1B and 1D, since we are not able to study them specifically [38].

Increasingly, the study of genetics is wending its way into our understanding of health and disease and offering new insights into treatment of various conditions. Though we are beginning to localize migraine to a relatively select array of genes, the implications for certain genes to be associated with migraine have yet to be translated to clinical applicability in migraine. Studies have characterized the gene expression responsible for age-related changes in the human brain using a post-mortem microarray. This has shown a consistent and selective portion of

between 5 and 10 % of the genome having age-regulated changes in expression levels in the brain. The most affected genes encode for the decreasing levels of neurotrophic factors BDNF and IGF-1, Calbindin, along with markers of synaptic density and neurotransmitter receptors for HTR2A and DRD2. There is also an increase in the marker of DNA damage, BCL-2 and of glial dystrophy including GFAP and NFk-B. The mechanism of these age-related changes is unknown. However, it has been hypothesized [39] that there is an age-related transcriptional program underlying these processes.

Conclusion

While migraine is believed to be a genetically determined hypersensitivity of the cortex at its root, we have little understanding yet of the putative genes linked to migraine and how they may relate to this process. We do know from other investigations that there are a small number of genes which are associated with age-related changes in their expression and their regulation of mechanisms which may be linked potentially to migraine. What determines their expression, however, is not understood but it has been hypothesized that there is a fundamental transcriptional program at work to set in motion the development of cells, maintain their health and also play a role in the degenerative aging process.

This may account for changes in the levels of neurotransmitters such as serotonin undergoing both evolutionary, maintenance and declining levels in much the same way as there are components of migraine which appear to evolve, stabilize, then decline such as overall prevalence rates and many of the associate symptoms of migraine.

However, there are other processes at work which may play a role in the lifetime changes in migraine. Evidence suggests that microglia need to be primed in order for them to express their role in modulating neurogenic inflammation at a later stage. This suggests that nature and nurture may both be at work in migraine. Even though the genes associated with migraine may be present, if the appropriate stimuli both early and again later in life are not present to invigorate the microglia, migraine may not occur or may not have the same implications for quality of life and headache characteristics in all patients equally.

Similarly, though we no longer accept Wolff's attempt to explain all of migraine from a vascular etiology, we continue to find ourselves pulled back to the blood vessel in migraine. This may be from explaining actions of medications and to accounting for the changes in endothelial health to regulate vascular processes related to age. It correlates physically and biologically with the changes in migraine and its expression such as the occurrence of aura with or without the headache as migraine patients age and are at risk for atherosclerotic changes.

So, the hyperexcitable brain may be one of hyperexcitable microglia. Having been primed to express their potential they play a major role in both the neurogenic inflammation, which is intimately linked to the pain of migraine, and also to contributing to the process of spreading depression, and with that the increase in migraine aura with age potentially. While the evidence suggests that spreading depression by itself is not responsible for the pain of migraine the activation of the glial cells in neurogenic inflammation may be the common pathway. Our understanding of the inflammatory process in the brain is incomplete and we know that a variety of T-lymphocytes and autoimmune chemical mediators may also be critical for the coordinated assault on the brain culminating with migraine and potentially contributing to the process of chronification as a separate process from the microglial cells. The damage to the microglia over the course of attacks from oxidative stress and the deposition of iron in the cells would normally be expected to make them less reactive to stimulation and engagement in the pain of migraine and which may again play a role, along with the changes in the blood vessels, to account for the diminished numbers of attacks of migraine with age. The role of other cells in contributing to maintenance of the neurogenic inflammation such as might be expected with an autoimmune contribution may account for the lengthening of the migraine episodes and perhaps of chronification of migraine. The WMH associated with migraine correlating with degenerative changes in the microglia as well as the inflammatory mediators and alteration of endothelia in migraine.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Frederick G. Freitag reported receiving consultancy from Transcept and honoraria from Allergan. Dr. Freitag reported receiving payment for the development of educational presentations including service on speakers' bureaus from Zegenix. Dr. Freitag is employed with the HealthTexas Provider Network.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.• Kurth T. The association of migraine with ischemic stroke. Curr Neurol Neurosci Rep. 2010;10:133–9. *Important paper looking at the factors involved in migraine related stroke.*

2. Bartleson JD, Cutrer FM. Migraine update. Diagnosis and treatment. Minn Med. 2010;93:36–41.

3. Stovner LJ, Zwart JA, Hagen K, et al. Epidemiology of headache in Europe. Eur J Neurol. 2006;13:333–45.
4. Wang SJ. Epidemiology of migraine and other types of headache in Asia. Curr Neurol Neurosci Rep. 2003;3:104–8.
5. Natoli JL, Manack A, Dean B, et al. Global prevalence of chronic migraine: a systematic review. Cephalalgia. 2010;30: 599–609.
6. Lipton RB, Hamelsky SW, Stewart WF. Epidemiology and impact of migraine. In: Silberstein SD, Lipton RB, Dalessio DJ, editors. Wolff's Headache and Other Head Pain. New York: Oxford University Press; 2001. p. 85–107.
7. Victor TW, Hu X, Campbell JC, Buse DC, Lipton RB. Migraine prevalence by age and sex in the United States: a life-span study. Cephalalgia. 2010;30:1065–72.
8. Bigal ME, Lipton RB. Migraine at all ages. Curr Pain Headache Rep. 2006;10:207–13.
9. Scher AI, Bigal ME, Lipton RB. Comorbidity of migraine. Curr Opin Neurol. 2005;18:305–10.
10. Meyer JS, Terayama Y, Konno S, et al. Age-related cerebrovascular disease alters the symptomatic course of migraine. Cephalalgia. 1998;18:202–8.
11. Robertson WM, Welch KMA, Levine SL, Schultz LR. The effects of aging on cerebral blood flow in migraine. Neurology. 1989;39:947–51.
12. Aiba S, Tatsumoto M, Saisu A, et al. Prevalence of typical migraine aura without headache in Japanese ophthalmology clinics. Cephalalgia. 2010;30:962–7.
13. Kelman L. The Aura: a tertiary care study of 952 migraine patients. Cephalalgia. 2004;24:728–34.
14. Headache Classification Committee of the International Headache Society. The international classification of headache disorders. Cephalalgia. 2004;24:1–160.
15. Silberstein S, Loder E, Diamond S, et al. Probable migraine in the United States: results of the American Migraine Prevalence and Prevention (AMPP) study. Cephalalgia. 2007;27:220–9.
16. Feleppa M, Bigal M, Lipton R. Headache in the elderly. Neurology. 2005;61 suppl 1:133–4.
17. Martins K, Bigal ME, Bordini CA, Speciali JG. Migraine in the elderly. Headache. 2006;46:312–6.
18. ••Bigal ME, Liberman JN, Lipton RB. Age-dependent prevalence and clinical features of migraine. Neurology. 2006;67:246–51. *A detailed examination of how migraine changes clinically with age across the lifespan*.
19. Wöber-Bingöl Ç, Wöber C, Karwautz A, et al. Clinical features of migraine: a cross-sectional study in patients aged three to sixty-nine. Cephalalgia. 2004;24:12–7.
20. Rostrup E, Gouw AA, Vrenken H, et al. The spatial distribution of age-related white matter changes as a function of vascular risk factors—Results from the LADIS study. NeuroImage. 2012; 60:1597–607.
21. Igarashi H, Sakai F, Kan S, Okada J, Tazaki Y. Magnetic resonance imaging of the brain in patients with migraine. Cephalalgia. 1991;11:69–74.
22. Murray ME, Vemuri P, Preboske GM, et al. A quantitative postmortem MRI design sensitive to white matter hyperintensity differences and their relationship with underlying pathology. J Neuropathol Exp Neurol. 2012;71:1113–22.
23. ••Turkoglu R, Tuzun E, Icor S, et al. Antineuronal antibodies in migraine patients with white matter lesions. Int Neurosci. 2011; 121:33–6. *First exploration of an uncharted area with significant implications*.
24. Tisserand DJ, van Boxtel MP, Pruessner JC, et al. A voxel-based morphometric study to determine individual differences in gray matter density associated with age and cognitive change over time. Cereb Cortex. 2004;14:966–73.
25. Rocca MA, Ceccarelli A, Falini A, et al. Brain gray matter changen migraine patients with T2-visible lesions A 3-T MRI study. Stroke. 2006;37:1765–70.
26. Sarchielli P, Alberti A, Baldi A, et al. Proinflammatory cytokines, adhesion molecules, and lymphocyte integrin expression in the internal jugular blood of migraine patients without aura assessed ictally. Headache. 2006;46:200–7.
27. Puente J, Jaque M, Carrasco C, et al. Triptan drugs, natural killer cell cytotoxicity, and neutrophils pro-matrix metalloproteinase-9 secretion. Headache. 2008;48:1482–9.
28. Vanhoutte PM, Scott-Burden T. The endothelium in health and disease. Tex Hear Inst J. 1994;21:62–7.
29. Bartley J. Could glial activation be a factor in migraine? J Med Hypotheses. 2009;72:255–7.
30. Bilbo SD, Smith SH, Schwarz JM. A lifespan approach to neuroinflammatory and cognitive disorders: a critical role for Glia. J Neuroimmune Pharmacol. 2012;7:24–41.
31. Grinberg YY, Milton JG, Kraig RP. Spreading depression sends microglia on levy flights. PLoS One. 2011;6:e19294.
32. Grinberg YY, Dibbern ME, Levasseur VA, Kraig RP. Insulin-like growth factor-1 abrogates microglial oxidative stress and TNF-α responses to spreading depression. J Neurochem. 2013. doi:10.1111/jnc.12267 [Epub ahead of print].
33. •Brown DR. Role of microglia in age-related changes to the nervous system. Sci World J. 2009;9:1061–71. *Very comprehensive examination of the work done to date on microglia*.
34. Welch KM, Nagesh V, Aurora SK, Gelman N. Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? Headache. 2001;41:629–37.
35. Ebersberger A, Schaible H-G, Averbeck B, Richter F. Is there a correlation between spreading depression, neurogenic inflammation, and nociception that might cause migraine headache? Ann Neurol. 2001;49:7–13.
36. Durham PL, Garrett FG. Neurological mechanisms of migraine: potential of the gap junction modulator tonabersat in prevention of migraine. Cephalalgia. 2009;29 Suppl 2:1–6.
37. Wenk GL, Pierce DJ, Struble RG, Price DL, Cork LC. Age-related changes in multiple neurotransmitter systems in the monkey brain. Neurobiol Aging. 1989;10:11–9.
38. Meltzer CC, Smith G, DeKosky ST, et al. Serotonin in aging, late-life depression, and alzheimer's disease: the emerging role of functional imaging. Neuropsychopharmacology. 1988;18:407–30.
39. Glorioso C, Sibille E. Between destiny and disease: genetics and molecular pathways of human central nervous system aging. Prog Neurobiol. 2011;93:165–81.