

# What is the evolutionary advantage of migraine?

E Loder

Headache and Pain Management Programs, Spaulding Rehabilitation Hospital, and Harvard Medical School, Boston, MA, USA

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## Introduction

Charles Darwin was beset throughout his adult life by recurrent, disabling headaches, and would today almost certainly be diagnosed as suffering from migraine (2). Yet there is no record that he ever speculated on what might be, as described by his theory of natural selection, the evolutionary advantage of migraine. By all accounts, Darwin was a retiring, methodical and somewhat obsessive man. A lifetime spent pondering a vast array of arcane, individual biological and fossil facts led him to the inescapable conclusion that larger forces were at work shaping the continual small changes observed over successive generations of all living things, including man. With him originated the now commonly accepted (but then radical) idea of 'heritable variability' in living creatures, with its implications of an unbroken chain of life extending back to a common ancestor for man and every other creature that ever lived.

Along with this Darwin developed what is often referred to as the doctrine of 'selection of the fittest': the idea that the forces of natural selection will favour traits that confer on their possessor the most 'fitness' for the environment. Creatures possessing different traits that adapt them more or less well to their environment will in consequence have different reproductive and survival rates. Even a trait that offers only a slight advantage will, over millions of years of evolution, be strongly selected for, while traits which reduce reproductive fitness even slightly will ultimately be eliminated.

Several lines of evidence make clear that susceptibility to migraine is to a large extent genetic, and therefore a trait upon which evolutionary forces must act. First, disease frequency varies from race to race -its prevalence is highest in Caucasians, intermediate in African-Americans and lowest in persons of oriental background (3). Second, the disorder is highly prevalent, affecting as many as 18% of women and 7% of men in the USA (4). Third, we have the identification of several different missense mutations on chromosome 19 that appear to be responsible in some families for familial hemiplegic migraine (FHM), a rare subtype of migraine with aura (5, 6). Mutations affecting this gene appear to alter the pore-forming and voltage sensor regions of neuronal calcium channels, with subsequent alteration of neuronal excitability (7). In some families with common forms of migraine, there also appears to be linkage to chromosome 19 (8). Recent research has suggested that variations in the dopamine D2 receptor gene may have some effect on susceptibility to migraine (9).

Although genetic factors play a necessary role in determining vulnerability to migraine, they are not sufficient to cause its development in all who inherit them. Twin studies, for example, suggest a heritability for migraine of around 40-50% (10). Thus, the evidence is that there are one or more genes, acting in combination with environmental factors, that produce susceptibility to recurrent, severe headache in response to various environmental triggers. Multiple different non-

specific, non-genetic and environmental factors would also seem to be implicated. These would act by affecting regulation of gene expression, could occur at any time and would influence brain development, function or anatomy. This interaction between inherited vulnerability and exposure to environmental triggering events probably accounts for many observations that have been made about migraine, such as its increased prevalence in those who overuse certain medications (11), have experienced head injury (12) or been exposed to early childhood trauma (13). It seems most likely that, from a genetic point of view, migraine will turn out to be similar to other multifactorial, non-mendelian and polygenic complex illnesses, such as schizophrenia.

How might the theory of evolution, with its concepts of natural selection and survival of the fittest, be reconciled with the facts as we know them about migraine? At first glance, it is hard to see how a vulnerability to recurrent, disabling headaches could possibly confer a reproductive or survival advantage on its possessors. Fitness-impairing disorders tend to disappear as a result of natural selection, and their frequency decreases to a rate approaching that of spontaneous mutation (around one in 50000 to one in 100000) (14). When this does not occur, it is important to consider whether the negative effects of the disorder in question are somehow counterbalanced by other advantages of the traits which lead to them. Few would argue that severe forms of headache disorders do not significantly impair fitness. Yet migraine has not disappeared over millions of years of evolution but is instead a strikingly common disorder whose prevalence, if anything, appears to be increasing (15-18). The possibility that this increased prevalence is due to methodological artefact has been deemed 'most unlikely'; changes in the social environment have been suggested as more probable (19). Even if its prevalence is not increasing, the very frequency of migraine, as well as the fact that it has been around since antiquity, imply that a central nervous system (CNS) susceptible to severe, intermittent headache must, at some point in human evolution, have conferred a hitherto poorly appreciated but important reproductive or survival advantage.

Although we speak in shorthand about genes 'causing' particular traits or disorders such as migraine, genes do not directly cause disease; rather, they determine only how an organism responds to the environment. Whether such traits are advantageous or result in 'disease' may vary depending upon the environment or situation. Thus, the important question about migraine is no longer whether or not it is genetically influenced, but why genes which lead to headache vulnerability persist. This question can only be answered by examination of the neurobiological and behavioural correlates of the migrainous genotype and consideration of their possible survival and reproductive advantages. While a detailed summary of the literature on this subject is beyond the scope of this article, it is clear that migraineurs possess a highly arousable CNS exquisitely sensitive to environmental input, especially that entering the trigeminal system (20).

On a clinical level, this inherited instability of CNS control systems that modulate environmental input results in a variety of manifestations, including an abnormal biological threshold to sensory stimuli. Among other things, migraineurs find unpleasant levels of light and noise that do not bother most people (21, 22), and demonstrate enhanced low-level visual processing with high speed in distinguishing visual targets (23). They possess a lower threshold for odour detection and lower thresholds for finding an olfactory stimulus unpleasant (24). Additionally, there is evidence that the CNS of migraineurs does not habituate to repeated sensory stimuli (25). Migraineurs also exhibit lower pain thresholds than controls (26), have lower tolerance of chronobiological challenges such as lack of sleep or skipped meals (27), and a tendency to develop headache in the face of emotional or physical stress (28, 29). It is also clear that migraineurs are more prone than controls

to develop depression, anxiety and other affective illnesses (30).

An exhaustive list of phenotypic correlates of the migraine genotype is impossible to generate, and undoubtedly many such features have yet to be identified. However, the theme that emerges from the limited information we do possess is that migraineurs are exquisitely responsive to a variety of environmental stimuli. This probably results in such behaviours as increased attention to environmental sensory stimuli such as light, noise and odours, an increased ability to detect and avoid threats in the environment, and a preference to avoid novel or unfamiliar (and therefore dangerous) environments. It does not require a great deal of imagination to generate hypotheses that account for these traits being favoured by the forces of natural selection, despite the fact that they are associated with a tendency to experience severe headache.

Randolph Nesse and George Williams have begun a branch of medical inquiry known as 'Darwinian medicine', which attempts to examine the possible adaptive value of genetic vulnerability to diseases. They have outlined five explanations that can account for apparently deleterious diseases and vulnerabilities being favoured by the forces of natural selection, and it is instructive to apply their evolutionary perspective to the question of migraine: 'The evolutionary explanations for the body's flaws fall into surprisingly few categories. First, some discomforting conditions, such as pain, fever, cough, vomiting and anxiety, are actually neither diseases nor design defects but rather are evolved defenses. Second, conflicts with other organisms *Escherichia coli* or crocodiles, for instance are a fact of life. Third, some circumstances, such as the ready availability of dietary fats, are so recent that natural selection has not yet had a chance to deal with them. Fourth, the body may fall victim to trade-offs between a trait's benefits and its costs; a textbook example is the sickle cell gene, which also protects against malaria. Finally, the process of natural selection is constrained in ways that leave us with suboptimal design features, as in the case of the mammalian eye' (14).

### **Migraine as a defence mechanism**

Let us begin by examining the idea that a tendency to develop head pain when faced with strong sensory stimuli or physical or emotional stress might be the result of an evolved defence mechanism. In reviewing this possibility, there are two possible explanations for painful headache: first, that headache pain itself is not advantageous, but simply an epiphenomenon resulting from other CNS processes that provide important evolutionary advantages. Alternatively, the headache pain itself might provide some benefit to the organism. In support of the latter hypothesis is the fact that the capacity to experience pain of other kinds has clearly evolved as a mechanism to encourage organisms to avoid potentially harmful situations. Individuals who are congenitally unable to feel pain generally die in early adulthood from tissue damage, joint destruction and other accidents (31). Viewed in this context, it seems possible that the pain of migraine might be a misunderstood defence mechanism that encourages the sufferer to withdraw from or avoid altogether situations which provoke headache. Since so many of the environmental triggering factors for migraine involve high levels of sensory, emotional or physical stimuli, one hypothesis is that the pain of migraine promotes aversion to novel or complex environments. During much of human evolution, withdrawal from a noisy, visually confusing situation might have decreased the chance of encountering or overlooking predators or other dangers. Over time, migraine-prone individuals would have 'learned' to avoid such situations in order to avoid the penalty of the painful headache that resulted from such exposure.

A related defence mechanism explanation for the characteristic increased sensitivity of migraineurs to olfactory stimuli and aversion to strong smells has been suggested, with speculation that perhaps olfactory migraine develops as an attempt to interrupt the entry of toxins into the brain, or to expel accumulated toxins arriving by this route. Unlike other cranial nerves, the cell bodies of the olfactory nerve lie within the structure of the brain. This anatomical arrangement permits toxins and viruses taken up by the olfactory nerve to be transported retrogradely to the dorsal raphe nuclei and locus coeruleus which interact closely with the trigeminovascular system (32). Likewise, the low threshold for nausea and vomiting that many migraineurs report might be explained as a mechanism to enhance elimination of ingested toxins in food. Researchers who noted a lower prevalence of malignant neoplasms in migraine patients compared with controls speculated that migraine might be protective against the development of tumours, although they acknowledged that the mechanism for such an effect is completely unknown (24).

There are still other ways in which a migraine-prone nervous system might provide a defence against potentially life-threatening situations. For example, the ease with which dilation of large cranial arteries can be triggered in migraineurs may actually be an important defence against vasoconstrictive emergencies that threaten brain survival. It has been suggested that 'the tri gemino-cerebrovascular system is a neurogenic mechanism capable of detecting and responding to crisis situations. When excessive vasoconstriction of the larger cerebral arteries threatens the survival of the CNS, a neurotransmitter, with calcitonin gene-related peptide (CGRP) as the most likely candidate, is released. This mechanism has important implications not just for cerebrovascular physiology but also in pathological states in man, where this view has received support in cerebrovascular disorders such as migraine and subarachnoid haemorrhage' (33). An accompanying editorial comments that the role of the trigeminovascular system 'would seem to be a neural protection system for the cerebral circulation, a neural vasodilator umbrella that protects against vasoconstrictor threats' (34). Here, the existence of painful headache may be an epiphenomenon rather than the object of natural selection.

By way of explaining why natural selection would tolerate and even favour such an easily activated defence mechanism system, Nesse and Williams invoke what they refer to as 'signal detection theory': 'Natural selection ... tends to shape regulation mechanisms with hair triggers, following what we call the smoke-detector principle. A smoke alarm that will reliably wake a sleeping family in the event of any fire will necessarily give a false alarm every time the toast burns. The price of the human body's numerous "smoke alarms" is much suffering that is completely normal but in most instances unnecessary. This principle also explains why blocking defenses is so often free of tragic consequences. Because most defensive reactions occur in response to insignificant threats, interference is usually harmless; the vast majority of alarms that are stopped by removing the battery from the smoke alarm are false ones, so this strategy may seem reasonable. Until, that is, a real fire occurs' (35).

In summary, then, it is not difficult to imagine ways in which an inherited low threshold for activation of the trigeminovascular system might be an evolutionary advantage, despite the inconvenience and suffering caused by the accompanying headaches. Even a small chance of protection from life-threatening dangers—decreased brain perfusion, predators, tumours, environmental toxins—could make the evolutionary cost of headache, painful as it is, cheap in comparison with alternatives. Most attacks of migraine can thus be viewed as the CNS equivalent of a burned toast setting off the smoke detector, with evolution deciding that the survival advantage

conferred by a low threshold of activation outweighs the disadvantage and discomfort of the headaches occasioned by many false alarms.

### **Migraine as a result of conflicts with other organisms**

To explain headache as a result of conflicts with other organisms is more difficult. For this hypothesis to be correct, a headache-prone CNS would be favoured by natural selection because it offers an advantage in dealing with certain infections or because certain pathogens benefit from the changes provoked by headache and have thus evolved to cause it. It is also possible that in some cases headache is a non-specific legacy of previous or latent infections that produce lasting alterations of brain structure or function.

How might a headache-prone CNS provide an advantage in dealing with infections? Headache, often with migrainous features, is a common accompaniment of many kinds of infections, particularly those of the CNS. Clinically, it seems that patients with a preexisting tendency to migraine are more likely to develop a severe headache in response to infections. Could headache in some cases be a mechanism that can help expel or kill infectious intruders? Perhaps the more easily triggered vasodilation in the CNS of migraineurs helps bring extra blood and infection-fighting cells to the brain to fight pathogens. If this is the case, we might expect that migraineurs deal more effectively than non-migraineurs with various CNS infections.

An alternative way to explain headache as the result of evolutionary conflict between organisms is to analyse matters from the point of view of the pathogen. Certain pathogens might have evolved to cause headache because it in some way acts to speed their transmission to other organisms. This is certainly the case with symptoms caused by other infections, such as the common cold, in which the sneezing and coughing resulting from the infection act to speed its transmission to other victims. However, there seems no plausible way to argue that pathogens might have evolved ways to trigger headache for this purpose, since headache causes sufferers to isolate themselves and withdraw from social interaction, thus limiting the chance they would infect others.

Yet another possibility is that migraine benefits neither the host nor the pathogen, but is simply the non-specific result of certain infections. This hypothesis probably deserves more consideration than it has had to date; while only a decade ago the idea that gastrointestinal ulcer disease might be caused by infection was dismissed out of hand, we now have incontrovertible evidence of an infectious cause in many cases (36). Initial reports linking primary headaches with *Helicobacter pylori* infection (37) have not been borne out by more careful subsequent studies (38, 39), but the possibility that at least some forms of migraine might be related to infections or their sequelae deserves further investigation. Amherst College biologist Paul Ewald has suggested that 'when diseases have been present in human populations for many generations and still have a substantial negative impact on people's fitness ... they are likely to have infectious causes' (40). He points out that there are probably only a few stereotyped ways for the CNS to respond to insults such as infection, with headache and seizures chief among them. Headache, perhaps mediated by autoimmune processes, could result from latent infections or infections whose effects continue even after they have been eliminated. Ewald suggests that in many cases, such a scenario would be

difficult to detect: 'By the time symptoms occur, the microorganism itself has disappeared, and its genome will not be detectable in any tissue ... Any time you have hit-and-run infections, slow viruses, lingering or relapsing infections, or a time lag between infection and symptoms, the cause and effect is going to be very cryptic'.

### **Migraine as a result of novel environmental factors**

Migraine could be a trait that natural selection has simply not yet had a chance to eliminate. Genes predisposing to migraine might have been less likely to lead to disabling headache during much of human evolution, whereas their interaction with modern environmental factors has amplified their tendency to cause disability and suffering. At least part of the increasing prevalence of migraine might thus be explained by interaction between the modern environment and a human nervous system that evolved in times of less sensory overload. Modern life is characterized by much more frequent exposure to many of the known triggers of migraine attacks than was the case during much of human existence. To name but a few, these include such things as bright light, loud noise, chronobiological challenges, altered sleep/wake patterns and emotional stress. We no longer live in caveman days, but given the immense periods of time required for evolution to act, correction of this mismatch between the human nervous system and the modern environment will necessarily lag behind the pace of environmental change by thousands or even millions of years.

### **Migraine as a compromise between genetic harms and benefits**

Migraine may represent a trade-off between a trait's benefits and its costs, in that individuals who inherit some of the genes associated with easy activation of certain brain stem nuclei enjoy survival advantages that outweigh the disadvantages experienced by individuals who inherit too many or too few of these genes. The benefits conferred by a trait do not have to be unmitigated in order for the trait to persist, and very harmful genes can persist if the advantages they offer in some individuals are sufficiently powerful. Here it is useful to compare headache with other genetically determined disorders such as sickle cell anaemia or cystic fibrosis. People with two copies of the sickle cell gene historically died young, while those with no copy of the sickle cell gene were more susceptible to malaria. Despite the suffering associated with both of the homozygous states, the sickle cell allele persisted and was selected for because of the advantage it provided to heterozygotes, who enjoyed a relative resistance to malaria. Similarly, heterozygotes for the cystic fibrosis gene were probably less likely to die of dehydration from common infections such as cholera or salmonella, thus ensuring that the gene persisted despite the high fitness costs suffered by those with two copies of the gene or none (41).

Applying this reasoning to the question of migraine, we can speculate that there should exist in the population a range of 'headache proneness', with people at one end of the spectrum who experience no headache, those at the other end who experience very severe and incapacitating headache, and the majority of the population falling somewhere between those two extremes. In fact, epidemiological evidence bears this out, with around 7% of men and only 1% of women reporting no experience of headache (42), and around 4% (almost entirely female) who have very frequent headache (31), with the bulk of the population between those two extremes.

The models provided by single gene disorders are oversimplified for our purposes, of course, since migraine is polygenic and multifactorial. They are principally useful as a way of

understanding how the multiple genes involved in determining headache susceptibility could be selected for if they improve the fitness of those who inherit them in moderate quantities. Here we are frustrated in our attempts to theorize by a lack of evidence about the fitness costs of migraine. Common sense and clinical experience indicate that those who suffer very frequent headaches (primarily women in their reproductive years), like those with two copies of the sickle cell gene, are severely disadvantaged. A completely neglected area of inquiry suggested by this premise is what the disadvantages are of having no headache. Although rare, such individuals exist, and evolutionary theory implies that one way of shedding light on the presumed evolutionary advantages of migraine would be to study carefully those whose nervous systems are incapable of generating it.

What we do not know is whether there is some advantage to what might be termed the 'headache heterozygote' state. Might those with mild forms of the disorder actually have enhanced survival? Certainly a modest dose of some of the things that go along with migraine—a heightened alertness to the environment—might be an advantage. There is evidence family members of subjects with migraine have enhanced visual sensitivity, though not as pronounced as that experienced by migraineurs (43). If sought, additional evidence of such intermediate phenotypes should be found.

The increased prevalence of migraine in women compared with men demands an evolutionary explanation as well. The documented influence of sex steroids in enhancing the expression of migraine genes (44) might be explained by the fact that migraine-linked traits such as aversion to novelty and avoidance of threatening environments were historically more important adaptations for women than for men. Throughout much of human history men have served as food gatherers and warriors, roles in which the expression of migrainous genes might reasonably be considered disadvantageous. In contrast, women were responsible for child-rearing, homemaking and food preparation, in which the behaviours associated with migraine expression such as sensitivity to environmental cues might have been an advantage in ensuring attention to the safety of children and the home. Additionally, the fact that migraine improves with pregnancy (45) might encourage more pregnancies among women with moderate forms of the disorder. It may be more than coincidence that the years of peak disease activity in women are between the ages of 25 and 40 (46), the period of life in which caring for offspring and ensuring a stable environment for them are most valuable. Or perhaps headache genes simply never decreased reproductive fitness enough to be selected against. If a lack of hormonal cycling protects against disease activity in migraine, the fact that our female ancestors spent most of their reproductive years pregnant or lactating may have limited the expression of the disorder.

### **Headache as a design constraint**

Because evolution can proceed 'only in the direction of time's arrow', the design of the CNS is constrained by what is already in place. Older brain-stem structures essential for survival are unlikely to be altered by the forces of natural selection, and cannot be redesigned 'from scratch' for perfect compatibility with more recently evolved brain structures. Drawing on recent evidence implicating brain-stem structures and dysfunction of pain inhibitory pathways in migraine (47), it may be speculated that disordered interaction between very ancient brain-stem structures and relatively newly evolved structures such as the neocortex is at the root of migraine. Brain-stem regions that are unable to suppress excessive input from higher brain centres might play a pivotal role in generating or failing to suppress an acute attack of migraine. As Goadsby puts it, 'instability

in the pain control system might mean that a continuous discharge might 'occur when subject to stimulation from higher centres (cortex, hypothalamus) as the result of stress or by excessive afferent input from the special senses or from cerebral or extracranial vessels' (48). To draw an analogy to the computer world, such a mismatch between older and newer structures might be seen as akin to the difficulties that occur when one attempts to use the latest printer or fax machine with an older and less advanced central processing unit.

Humans appear to be the only species in which anything remotely resembling migraine is common and occurs on a regular basis. Given that our DNA differs from that of the great apes by only a few percentage points, the relevant question is why this is so. It is tempting, but probably incorrect, to ascribe the lack of an animal model for migraine to the fact that animals cannot communicate to us the experience of headache, or to suppose that we are unable to recognize headache in animals. By analogy with other pain states, it seems unlikely that the non-verbal behavioural correlates of headache (head holding, social withdrawal, vomiting, marked aversion to light and noise) would differ significantly in apes compared with humans. In fact, 'there are uncanny similarities in the non-verbal communication patterns of chimps and humans kissing, embracing, patting on the back ... and these patterns appear in similar contexts as those in which they are seen in humans' (49).

It seems even more unlikely that headache-related behaviour, if common, would escape notice or comment, especially given the level of scrutiny to which our closest ape relatives have been subjected (Jane Goodall's lifetime study of chimpanzees, for example). Yet only two such accounts could be located, the first of a great ape at the Toronto Zoo, who periodically held her head and appeared sensitive to light (50). The second report is of an orangutan in the Borneo rain forest, who was 'clutching her head and groaning, only to make a complete recovery after eating some flowers from a nearby bush'. (The naturalist who observed this episode later treated his own headache with the same purple *Fordia splendissinia* flowers and 'within 15 min my headache was gone' (51).) While we cannot disregard these reports, the fact that there are so few of them provides further support for the view that recent evolutionary changes in the brain may underlie our species' peculiar susceptibility to migraine.

Superior cognitive abilities and a well-developed awareness of self and environment most distinguish humans from our ape relatives. The human brain stem thus must cope with the additional challenge of input from newly evolved cognitive processes as well as other sensory and vascular information. It may be this extra burden which periodically overwhelms older brain-stem structures and renders the human species so vulnerable to migraine. In all likelihood, the same changes in brain function and structure that make possible self-awareness and intelligence are those that predispose us to migraine. Thus, a vulnerability to recurrent headache may be the price we pay for consciousness. To paraphrase Descartes, 'I think, therefore I have migraine'.

## **Summary**

An evolutionary view of headache and its biological and behavioural correlates suggests the right questions to ask about migraine and its persistence over millions of years of evolution. The process of natural selection, acting upon the countless CNS variations offered up at random by nature, has settled on genes which promote easy activation of the trigeminovascular system. While



some of the hypotheses examined in this paper may seem fanciful or far-fetched, they help to illustrate the way in which we should be thinking about migraine in the context of evolution. Many of the clinical manifestations of the migraine-prone nervous system might then be recognized as adaptive, even in the face of the costs associated with an increased susceptibility to headache.

It is noteworthy that the theory of evolution, which provides the fundamental explanation for the existence of migraine, may in part owe its origin to Darwin's own headaches. For although he was never moved to speculate on the broader evolutionary advantages of headache, it is clear that headaches provided Darwin with a socially acceptable reason to, avoid many unwanted social and academic obligations. The consequent lack of distraction provided time for the lengthy reflection, reading and synthesis of ideas necessary to discern the fundamental organizing principle of all life.

'It was the life of an invalid and what freedom it brought! Charles Darwin never sat on committees, never went to official dinners, saw only the people he wanted to see, read only the books he wanted to read. Philosophy and religion he found brought on a headache at once. As the great man lay on the sofa he was not idle. His mind was at work, and it was in those long hours of silence and solitude, lying on his sofa, meditating, that Darwin reached his bold conclusions. He himself expressed his most valuable quality as "unbounded patience in long reflecting over any subject". For his long reflecting he needed his sofa.' (52)

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