Migraine Headache: A Precursor to Alzheimer's Disease?

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Abstract

The hypothesis proposed by this paper is that those who suffer from migraine attacks in adolescence and adulthood (especially women) may be likely to develop Alzheimer's disease as they age due to genetic, pathological and chemical similarities in the progression of each disorder. In defining each illness, listing symptoms and clinical characteristics that are commonly seen in each, and comparing the two, this research hopes to illustrate that there is enough evidence linking these illnesses that further research on the subject should perhaps be done.

INTRODUCTION

Could migraine headache be a precursor to Alzheimer's disease? There are several aspects that are similar, if not the same in the processes of both illnesses. Risk factors common for patients suffering from each disorder include visual dysfunction, depression, lethargy, mood changes, sense of pain to non-painful stimuli, inability to produce purposeful coordinated movements, and in women changes in ovarian hormone levels. The neurotransmitter systems and inflammatory processes throughout the body are directly related to variations in estrogen and progesterone levels. Estrogen, particularly, has a profound effect on the central nervous system (Martin & Behbehani, 2006). This promotes the fact that women are more likely than men to develop either migraine attacks, Alzheimer's disease or both. If the symptoms and clinical manifestations are recognized early on, hormone replacement therapy as well as other medication therapies can be used as a treatment of and preventative for MA and AD (Fillit, 2002) & (Martin & Behbehani, 2006).

LITERATURE REVIEW AND DISCUSSION

Migraine headaches are recognized by the World Health Organization as one of the most debilitating neurological disorders, affecting between ten and twelve percent of the population. Typically migraines present with intense pain that predominates frontally with one side of the cranium being affected more so than the other, although attacks can be bilateral as well. These episodes of migraine can be incapacitating and are often accompanied by nausea and vomiting and sensitivity to light and sound (Vincent & Hadjikhani, 2007). Other symptoms associated with migraine include dizziness, vertigo, blurred vision, aversion to particular smells as well as ataxia. Migraine can occur with or without aura. Aura, believed to be caused by changes in blood flow, are neurologic episodes manifesting as visual oddities that have been described as mirrors or flashing lights, this according to http://adam.com. Triggers of attacks differ among migrainuers. Stress, food sensitivities, exercise, noxious odors and temperature variances are some of the more common triggers covered in medical literature.

The specifics of migraine origin remain controversial, hypothesized on but for the most part, remain unexplained. Three of the most popular theories of migraine pathology credit genetics, cerebral vascular defects or neural hyper-excitability. Any of the three result in cortical spreading depression (CDS) which is a “slow self propagating wave of neural and glial depolarization followed by long lasting suppression of neural activity. CDS has been directly demonstrated in humans suffering from brain trauma or cerebral hemorrhage,” (Granziers, DaSilva, Snyder, Tuch & Hadjikhani, 2006). Presently, there are no specific biomarkers that enable the conclusive diagnosis of migraine (Granziera, DaSilva, Snyder, Tuch & Hadjikhani, 2006).

Not unlike migraine, another neurological disorder, Alzheimer's disease, is an exceptionally difficult diagnosis for medical care providers to make. Worley, (1998), described AD as a “dehumanizing condition of degenerative memory loss and physical deterioration which ultimately leads to death.” More specifically, Alzheimer's disease (AD) is the most common cause of dementia among the elderly

with clinical presentation that includes, but should not be limited to, insidious short then long term memory loss, language imparities, inability to recognize familiar people or settings, difficulty drawing simple objects, inability to produce coordinated movements, unfocused thinking and poor judgment (Yaari & Corey-Bloom, 2007). Although several theories of the pathogenesis of AD abound, there is no unanimously accepted explanation of cause for the disorder. Several risk factors have been identified as predisposing entities for AD. According to Yaari and Corey-Bloom (2007), a positive family history is the most prominent risk factor for the development of AD this is second only to progressing age.

DISCUSSION

Having established the basis of both migraine attacks and Alzheimer's disease, a comparison of each disease course, symptoms, and their clinical findings can be made. As mentioned previously, migraine is recognized as a neurological disorder, but studies have shown that like Alzheimer's disease, migraine headaches may be a neurodegenerative process. Neurodegeneration, for the purpose of this paper, will be defined as any process or structural defect that causes insult to or death of cerebral tissue. AD is an established neurodegenerative process in which every part of the cerebral cortex is affected. Definitive diagnosis of AD can only be made at autopsy where due to cerebral vascular inadequacy, a reduction in the number of Purkinje cells are found (Baloyannis & Costa, 1997). More classic findings are atrophic tissue, white matter lesions, loss of synapses, neuritic plaques and neurofibrillary tangles (Yaari & Corey-Bloom, 2007). Similar cerebral findings are reported in patients with a history of migraine. Vincent & Hadjikhani (2007) reported that autopsies of patients with a history of migraine attacks have shown cerebellular atrophy, cortical cerebellular degeneration and loss of Purkinje cells.

A study on migraine attacks by the University of Rochester Medical Center reported in 2007 that cortical spreading depression, the underlying mechanism of migraine pain, is linked to hypoxia, loss of neurons, and cerebral synaptic changes. Further similarities in cerebral alterations are the prevalence of white matter lesions in both diseases. It should be noted, however, that in AD the lesions or tangles are attributed to components of tau protein (Yaari & Corey-Bloom, 2007), where as Kruit, Buchem, Hofman, Bakkers, Terwindt, Ferrari & Launer (2004), give no specific causative factor for lesions found in migrainuers. Although the pathogenesis of the white matter lesions found in migraine patients are unknown, they are thought to be linked to the possible vascular components of the disorder. Lipton and Pan, (2004) suggest that removal of white matter lesions in migraine may be a therapeutic option. It would seem reasonable to assume that lesions may be removed in Alzheimer's patients as well. Cardiovascular disease (CVD) and cerebral vascular disease are a commonality between MA and AD. One of the most compelling, however, recently challenged theories on the origin of migraine is that fluctuations in blood flow through the cerebral vasculature is to blame for the dizziness, inability to produce coordinated movements (ataxia), poor articulation (dysphasia) , and aura that are commonly reported in attacks (Vincent & Hadjikhani, 2007). Cardiovascular disease is a co-morbid factor in all vascular dementias as well as Alzheimer's disease, which is theorized to have a significant vascular component (Baloyannis & Costa, 1997). CVD in the form of transient ischemic attacks, stroke and infarcts are findings in the cerebral tissue of Alzheimer's patients as well as those patients with a history of migraine headaches (Kriut, van Buchem, Hofman, Bakkers, Terwindt, Ferrari, & Launer, 2004) & (Edwards, 2006). Another interesting finding that is common in the two disease processes is that many times patients of both will have right-to-left shunting due to an atrial septal defect known as a patent foramen ovale (PFO). A patent foramen ovale is the remains the foramen ovale of fetal circulation which allows blood to flow from the right to left atria of the heart. Siberstein (2006), reports that “moderate to large right-to-left shunts, most of which are PFO's are extremely common in patients who suffer from migraine with aura. According to Purandare, Voshaar, Burns, Velupandian & McCullum (2006), Alzheimer's patients are often found to have PFO's as well. Micro thrombi reportedly pass through the PFO in Alzheimer's patients and usually go undetected until autopsy.

Lastly, vascular inflammation is common in both AD and MA. Postmortem studies find that the brains of AD patients generally show chronic inflammation. This inflammatory response is to mutated proteins being deposited within the cerebral vasculature (Fillit, 2002). Migraine headache has also been attributed to an inflammatory response to cerebral vasculature dilation. The inflammation in this case is due to peptide deposition (http://www.adam.com). Inflammation within the cerebral vasculature increases the likelihood of ischemic stroke of which migraine is a known risk factor, especially in women (Lipton & Bigal, 2006). In turn, ischemic stroke is a known risk factor for all types of dementia, including AD (Purandare, Voshaar, Burns,

Velpandian & McCollum, 2006). This is another potential connective factor in the disease processes.

With little knowledge of either disease progression, one could say with near certainty that both MA and AD are genetically determined diseases. Historically, migraine attacks have been attributed solely to cerebral vascular deficits. While this may be one component of the disorders pathology, genetics play a major role in the process as well. Gene mutations are likely to cause a majority of migraines according to http://www.adam.com. Yaari and Corey-Bloom (2007), state that a positive family history is the most outstanding risk factor for the development of AD this is second only to progressing age and is "inherited in an autosomal-dominate manner." Wikipedia states:

The chances of an autosomal dominant disorder being inherited are 50% if one parent is heterozygous for the mutant gene and the other is homozygous for the normal, or 'wild-type', gene. This is because the offspring will always inherit a normal gene from the parent carrying the wild-type genes, and will have a 50% chance of inheriting the mutant gene from the other parent. If the mutant gene is inherited, the offspring will be heterozygous for the mutant gene, and will suffer from the disorder. If the parent with the disorder is homozygous for the gene, the offspring produced from mating with an unaffected parent will always have the disorder.

Most pathophysiological theories count genetics as a predisposing factor in MA as well (Vincent & Hadjikhani, 2007). The medical community has made significant strides in identifying that gene mutations on several specific chromosomes are prevalent in Alzheimer's patients. Three genes in particular can be traced to ninety percent of cases of early onset AD. These genes and their host chromosomes are: presenilin-1 on chromosome 14, presenilin-2 on chromosome 1 and the amyloidal precursor gene on chromosome 21. The amyloidal protein is responsible for the neurofibrillary tangles or lesions seen in AD autopsies. White matter lesions are also found in migraine patients, the amyloidal precursor protein may be the casuistry factor in the development of these findings also. Chromosome 19, the carrier of ApoE is responsible for the most typical, sporadic form of AD. Chromosome one is one of the carriers of the defective genes seen in AD. A recent study shows that chromosome one, in some migrainuers, carries a gene that predisposes them to MA (Reilly, 2004). Although little literature exists on genetics as it relates to migraine attack, the strong familial relevance of the disorder calls for further research on its ties to gene mutation. The only common finding in this area is that chromosome one is a carrier of defective genes in both illnesses.

It is documented that women are three times more likely to have migraine headaches (Martin, 2006) and one and a half times more likely to develop Alzheimer's than are men (Fillit, 2002). This could be due in part to ovarian hormone fluctuation and cessation at menopause. Ovarian hormones, particularly estrogen, play a significant role in neurotransmitter regulation throughout the central nervous system. Several neurotransmitter systems are effected by and play significant roles in AD and MA. Neurotransmitters are chemical messengers that relay signals between neurons and other cells. Estrogen fluctuations in women who suffer from migraine attacks may benefit from hormone regulation therapy such as oral contraceptives or herbal medications. Estrogen enhances neurotransmission, production and regulation in the central nervous system. This is true in women with AD as well Cessation of estrogen production after menopause is thought to be an important factor in the Alzheimer's process. Although further research is necessary, Zandi, Carlson, Plassman, Welsh-Bohmer, Mayer & Steffens (2002), suggests that hormone replacement therapy may reduce a women's risk for developing AD (2002). Transmitter systems affected in both disorders include the cholinergic, serotonergic, glutamatergic, dopaminergic, noradrenergic and GABAergic systems. All of these systems are interrelated and are affected by other chemical processes in the body. The cholinergic system, along with other along with other analgesia systems is defective in migrainuers (Nicolidi, Galeotti, Ghelardini, Bartolini & Sicutari, 2002). In AD the "most consistent neurochemical change… has been the well documented decline in cholinergic activity," (Yaari & Corey-Bloom, 2007). Although the product of the cholinergic system, acetylcholine (ACh), cannot be measured accurately, a functional decline in the cholinergic system is apparent in the form of impaired motor coordination in patients with AD (Gsell, Jungkunz & Reiderer, 2004).

The functional decline of the cholinergic system to produce acetylcholine directly alters the production of serotonin, another neurotransmitter that affects feelings of well being and sleep patterns. Serotonin levels in women who suffer from migraine may be low due to fluctuations in ovarian hormone levels. Estrogen increases production, while decreasing the degradation and reuptake of serotonin (Martin & Behbehani, 2006). Low serotonin levels are suspected to

be a causative factor in AD as well (Gsell, Jungkunz & Reiderer, 2004).

Melatonin is a byproduct of serotonin. Melatonin production may have an analgesic affect in those who experience migraine. The anti-inflammatory properties of melatonin are well documented; however, several studies have shown that here are insufficient levels of melatonin in migraine patients (Volger, Rapoport, Tepper, Sheftell & Bigal, (2006). The fact that decreases in serotonin correlate to decreases in melatonin would suggest that AD patients have lower levels of melatonin than patients without the disease, and are not benefiting from the anti-inflammatory properties thereof. Martin states that GABA is the major inhibitory neurotransmitter in the CNS (2006). GABA, like the other neurotransmitters mentioned are affected by estrogen levels and are likely to be casuistry factors in both disease processes (Gsell, Jungkunz & Reiderer, 2004). GABA and glutamate are most likely to be increased in patients with MA and those with AD. Glutamate is the primary excitatory transmitter and is likely to contribute to "AD through excito-toxicity," (Fillit, 2002). Increased glutamate as it pertains to MA leads to rapid neural firing (excitability) and cortical spreading depression which is one of the theories of migraine pathology.

It should be noted that the hypothesis that similarities in neurotransmitter abnormalities in MA and AD are based on the effects of estrogen on the CNS. This hypothesis pertains solely to women as there were no studies found on the affects of male gonadal hormones on the CNS and neurotransmitter systems.

A final commonality between MA and AD are the theories that suggest that abnormalities in calcium levels and/or calcium channels are responsible for the pathology of each illness. Calcium, the most prevalent mineral in the body, has a critical role in most cellular processes. Ideally, the levels of calcium within the cell are low, as it is continually removed by buffering mechanisms. In the common migraine headache, it is theorized that the abnormalities in the calcium channels themselves are at fault. The release of serotonin (which is established to be affected by estrogen) is regulated by these channels, magnesium, which is known to be low in patients with migraine, plays a part in channel function, and these channels effect cortical spreading depression, which has been described previously. In a rare type of migraine, familial hemiplegic migraine (FHM), the mutation of the CACNA1A gene is interferes with calcium channel functioning causing an abnormal release of calcium. This encoding gene plays a major role in the release and regulation of calcium as well as neurotransmitters at the neural synapses (Hoffman, 2001). With an over abundance of calcium within the cell, potassium is released into the extracellular fluid. The upset in potassium levels affects regulation of glutamate, the primary excitatory neurotransmitter (Fillit, 2002), which in turn causes cortical spreading depression. This hyper-excitable state may result in common feature often associated with migraine such as aura, which is generally thought to be related to cerebral vascular defects, and trouble with motion processing (Granzieria, DaSilva, Snyder, Tuch & Hadjikhani, 2006). Whether defective calcium channels or the effects of mutated genes on these channels are at fault, the result is calcium toxicity which leads to an "excitable brain" and cerebral atrophy in some migraine sufferers (Hoffman, 2001).

Studies by the Sanders-Brown Center on Aging at the University of Kentucky revealed that calcium toxicity in Alzheimer's patients is due to lipid peroxidation. This process impairs the protein function of the cell membrane which is, with in a normal cell, the removal of calcium from the intracellular space. The result is a increase in calcium within the cell, this causes a hyper-excited state and leads to neural death (Worley, 1998). This, as described by Fillit (2002), is an excito-toxicity, and has been explained previously in the calcium toxicity theory of migraine origin, the difference being the principle mechanism of accumulated calcium within the cell.

In conclusion, there are many factors that are common among sufferers of Alzheimer's disease and those who suffer from migraine attacks. These commonalities may suggest that those who suffer from migraine attacks in adolescence and adulthood (especially women) may be likely to develop Alzheimer's disease as they age due to genetic, pathological and chemical similarities in the progression of each disorder. Findings of an association between the two disease processes could help lead to earlier diagnosis of AD. Early diagnosis can help reduce or delay some of Alzheimer's most devastating effects. The intent of this paper is to prod further research on the possibility that migraine may be a predisposing aspect of Alzheimer's disease.

Upon completion of this paper, I feel that I have learned a great deal about the disease processes of both migraine and Alzheimer's disease. I started this research on the supposition that there was a possibility that Alzheimer's patients may have a history of migraine attacks (my paternal

grandmother had migraines as a young woman and now suffers from Alzheimer's). I wanted to find out if there were any factors that were similar in the two disorders because I also have migraines, so I wanted to know if there could possibly be a familial tie to the two. I found many similar characteristics in the clinical findings, but no definitive genetic linkage. I hope that there is enough information that associates the illness that someone will pick up the research and perhaps find a way to diagnose Alzheimer's earlier. Most medical literature concedes that the earlier the disease is diagnosed, the better the chances to slow symptom progression. I regret that someone had not thought of this sooner, I may just be digging, but it seems as though there could be some credence to what I found.

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