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Review Article

Migraine headaches as a preliminary symptom for cognitive decline

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Abstract. Migraine headaches are amongst the most prevalent neurological disorders. Dementia on the other hand, is classified as a neurodegenerative disease with symptoms of slow progressive memory loss and cognitive decline. Identifying the preliminary signs and symptoms of such neurological diseases are crucial in preventing the onset of such disease. In this review article, we analyzed several studies signifying and or contradicting the claim of migraine headaches as a preliminary symptom of dementia. This can ultimately aid in focusing specific treatments to reduce the risk of patients developing dementia. Databases including Google Scholar, PubMed, and NCBI were searched by using keywords including migraine, dementia, association, symptom, etc. This study analyzed articles that were sought through various databases. Several studies signified a positive correlation between the two diseases. Studies that contradicted this claim, were vastly outnumbered by studies that depicted the claim to be true. It was eminent that preventing and treating migraine headaches in patients with a high-risk profile of dementia should be considered and studied more extensively.

Keywords: Migraine, dementia, cognitive decline, neurodegenerative disease, headache

Introduction

Headaches, affect 46% of the world population [1]. They are considered as the leading cause for outpatient and emergency department visits [2]. Migraine headaches are defined as headaches lasting four to 72 hours with symptoms including unilateral location; pulsating quality; moderate to severe intensity; intensified by physical activity; occurrences of nausea, vomiting, phonophobia, and or photophobia [3]. The epidemiological burden of this disease has been observed to have a greater portion allocated to women. In a study conducted by Rebeca et al. a significant 2-fold difference was present when comparing females and males that showed symptoms consistent with Migraine [4]. Migraine headaches were also observed to have a maximum 33% prevalence in Asian countries as compared to 9% in western pacific countries such as China [3]. The variable prevalence in certain areas can be denotive of the cultural and dietary attitudes effective in causing Migraine headaches. The third most prevalent disorder that was suggested by the Global Burden of Disease study conducted in 2010 was Migraine headaches. Currently, it is suggested that 35 million American are victims of the mental disorder and suffer from migraines in a variety of ways [2].

Migraine Headaches

The pathophysiology of migraine headaches has advanced over the previous decades. Current studies now point out peripheral nerve compression and or traction as the etiology of the disease. These compressed nerves can be found throughout the head and even the neck region. Migraine, can be considered an inherited, episodic disorder that is assisted with sensitivity of the ear and light receptors. The common symptoms and complaints include a throbbing headache, nausea, and vomiting. Dizziness and light headedness can also be noted in patients as many complain having a feeling of being drunk or have stepped off a boat. The nervous pathways allocated to cerebral pain include the ophthalmic branch of the trigeminal nerve (CN V), a sensory nerve that receives input from the orbital region. The facial nerve also consists of sensory fibers that perceive pain from the maxillary area [5].

Dementia

Dementia, a general term which incorporates several diseases that cause a loss of function or cellular death in the Central Nervous System (CNS).As studies suggest, the behavior, memory and even personality of the patient are susceptible to change. Finding the main etiology and or the reason for such neurodegeneration can aid in treating the patient in a proper and rapid manner, limiting the adverse effects it could have on the patient. The chances of reversing the neurodegeneration and trauma in dementia is minimal and can be allocated to 9-11% of cases [6].

There are several forms of dementia, most of which are based on their primary cause, which include Alzheimer's disease, Vascular dementia, Frontotemporal dementia, dementia with Lewy bodies, and mixed dementia [7, 8]. All

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types of dementia ultimately lead to neurodegeneration and an inability to fully use one's cognition. Memory loss, personality change and an inability to properly process environmental phenomena are severe symptoms of dementia which if not treated can possibly lead to a shorter life time [9-11].

The Association between migraine headaches and dementia has been focused on in many studies. However, a vague conclusion for migraine headaches as a preliminary symptom of dementia still exists as many factors must be taken into consideration [12]. In this study, we review the existing literature for commonalities and relations between both mental discrepancies.

Materials and Methods

Search strategy included identifying Mesh terms and Keywords (i.e., Migraine, Dementia, Association, Symptom, etc.) and conducting an advanced search in databases such as Google Scholar, PubMed, and NCBI. Results were screened based on criteria and were selected for data extraction.

Results and Discussion

Migraine is considered to be a recurrent primary headache disease [93]. Several studies have demonstrated that migraine prevalence can range from 6 % to 13%. This headache disorder affects nearly 18% of the women population as well as 6% of the male population [41]. Furthermore, it has a pulsating attribute and usually lasts from a couple hours to 3 days [94]. Migraine can cause vomiting, nausea, sensitivity to smell and light as well as aura [95, 96]. Also, physical activity has been observed to worsen the situated pain [97]. This as a result, leads to limitations in a vast variety of activities, ranging from everyday chores to profession related tasks. Moreover, approximately 12% of individuals suffer from migraine, including 6% of men as well as 18% of women [98]. In other words, it is the third most common and prevalent global disease [108]. Nevertheless, both environmental and genetic factors trigger migraine [99]. It can be induced by hormonal changes in the body, for instance, girls tend to have more migraines after puberty as significant hormonal changes are eminent [107]. It is estimated that migraine is seen more in women as compared to men [100, 101]. Nonetheless, medications such as beta blockers, topiramate and sodium valproate are efficient in decreasing the pain [102].

The tension type headache (TTH) is considered the most prevalent kind of primary headache which comes along with mental tension and pain in the cerebral area. Also, this type of headache is not correlated to physical activity as it does not change when heart rate, blood pressure and or endocrine stimulation occurs [13]. This is true whilst the intensity of migraine is more severe than TTH [14]. On the other side recent evidence demonstrate an association between headache and dementia, while most studies are circulated around migraine [15-22]. Dementia is considered to be one of the most prevalent types of neurodegenerative diseases that has a huge effect on the quality of life [23]. Its symptoms are variable and include slow memory impairment, headache, and change in personality etc. [24]. Nearly 24.3 million people have been diagnosed with dementia globally, this number is expected to jump to 81.1 million people by the year 2040 [25].

There are several kinds of dementia that have been identified. Amongst them, non-vascular dementia (such as Alzheimer's disease (AD) is known to be the most common type, which makes up 80–90% of present cases [26, 27]. The risk of dementia increases with age, a variety of comorbidities, including hypertension, diabetes, dyslipidemia, heart failure (HF), ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), head injury, depression, Parkinson's disease and stroke [28-32]. The association between somatic symptoms, like headaches, and clinical symptoms, is assumed to be more than a simplistic coincidence [33].

Several cohort studies have previously suggested a connection between migraine and dementia [34, 35]. Nonetheless, the results of other studies on migraine and cognitive disorders were controversial and mixed, with some of them failing to find any direct association. In most countries, Alzheimer is assumed to be the most common cause of dementia in senior citizens [36]. Women tend to contract Alzheimer's disease approximately two times as much as men do. Which is induced by the fact that women tend to have much more life expectancy than men [37].

Numerous analyses imply that incidence rates are higher in older patients. Neuroprotective precautions along with estrogen effect on b-amyloid formation and basal forebrain cholinergic neurons appear relevant to the treatment as well as Alzheimer's disease prevention. There is insignificant clinical support concerning whether estrogen has a part in treating Alzheimer or not, such as a year-long research conducted over 120 hysterectomized ladies in United States, where the interventions were unopposed conjugated equine estrogen [38] and or a 7-month research of 117 females in France, where the intervention applied was transdermal estradiol along with, oral micronized progesterone [39]. Primary results of WHIMS published in 2003 signified dementia as primary cause [40].

Nevertheless, migraines increase the risk of brain lesions statistically [42]. More recent research has associated brain lesions to incidence of cognitive decline and dementia. As a result, migraines might signify a positive correlation and a progressive brain disease [43]. Several studies have also contradicted such, and have shown no significant link between migraine and dementia [44, 45, 46]. This is, while others, proved cognitive function to decline amongst individuals with migraine [47, 48, 49]. A study from a valid national database showed that migraines end up in a higher risk of developing dementia in future by adjusting for hypertension, diabetes, depression and head injury, CAD, all of which, are able to boost the risk of dementia in patients suffering from migraine [50]. In Asia, migraine headaches are the most common kind of headache that is diagnosed in walk in clinics [51]. The prevalence of migraine headache is 6.5% in men and 18.2 % in women in the USA, as well as 7.5% and 16.8 %, respectively in Europe [52, 53]. People with migraine exhibit a high risk of vascular diseases due to the fact that migraine headaches, in nature, are a neurovascular dysregulation disorder [54, 55]. Nevertheless,

a theory about migraine mechanism demonstrates that the abnormality in electrophysiological activities of the cortex is of great importance in migraineurs [56, 57]. Epilepsy is another disease associated with the brain function, which is more severe than migraine, with a 0.5-1% prevalence rate globally [58, 59]. Seemingly, epilepsy and migraine have been assumed to be comorbid diseases for decades [60, 61]. It is estimated that 46 million individuals have dementia worldwide [62]. As the population ages, incidence rates of dementia may continue to rise [63]. However, there is no effective treatment for this condition. Investigations have shown that migraine affected approximately 1.04 billion people worldwide [64]. The overlap of biological mechanisms between dementia and migraine, including brain microstructural changes, neuro-inflammation, and subcortical white matter disorders [65-68]. This shows that migraine might elaborate the risk of dementia.

On the other hand, recent studies that claim a link between dementia and migraine demonstrated inconsistent connections [69, 70]. Although many researches have suggested a possible association between dementia and migraine, there are concerns that these links be due to unmeasured, confounding or diagnostic bias. Although, the MGRS was significantly related to migraine ($p < 0.0001$), there was not any association between migraine and dementia [71].

Nevertheless, many studies found variable results such as Chabriat et al. [72] in a case study, where 8 cases of Dementia were collected as case reports and were analyzed to signify various symptoms. All of 8 patients were related as primary, secondary, or tertiary family. Each patient had separate diagnosis at various times and were cared for separately. Case reports from all 8 patients were summarized and compared in terms of symptoms such as headaches, fever, neurological disorders and etc. This study specifically focused on the outcome of common symptom findings amongst many patients. The Migraine headache was observed in 6 of 8 cases, which was included using IHS classification criteria for the disease. The patients were remarkable for the great frequency of throbbing headaches. In all but one patient focal neurological symptoms were present preceding headaches, gradually developing over a course of 5 to 15 minutes. 7 of 8 patients were found to have nausea and vomiting alongside their headaches. Thus, such symptoms were seen in almost all of 8 patients with diagnosis of dementia. Migraine headaches were noted as a cause for many of their symptoms including nausea, vomiting as well as neurological defects [72].

Finsterer [73], in a review article sought to observe cognitive decline alongside mitochondrial disorders. Respiratory chain disorder (RCD) was the prominent subject of discussion and was analyzed in different aspects. Various symptoms including Dementia, ataxia, migraine headaches and etc. were observed in most cases. RCD was prominent alongside other diseases such as Leigh syndrome, KS syndrome, and MELAS. As discussed in the review article, RCD diagnosis was based off symptoms such as cognitive impairment, neurological impairments, as well as dementia. A major tip off symptom for RCD diagnosis was considered to be migraine headaches with improper and short stature. A vague but present bond was noted between dementia and migraine headaches [73].

The most common cause for dementia is Alzheimer's disease [74]. Thus, the comorbidity profile in dementia with Lewy bodies (DLB) compared to Alzheimer's disease was studied by Fereshtehnejad et al. in a detailed format [17]. Information and data were sourced from the Swedish dementia registry as well as the National Patient Registry. This linkage study over saw 634 patient profiles with DLB and 9161 patient profiles diagnosed with AD between the years 2007-2021. Migraine diagnosis as a symptom was defined according to ICD version 10 codes. Taking into factor the timing of events, migraine and depression were more commonly significant preliminary to the diagnosis of DLB. Migraine headaches were seen more prominently in the DLB group as compared to the AD group. However, a minimal amount of 6 patients of the 634 were seen to have such headaches. Alongside migraine headaches, depression, stroke, and cerebrovascular infarctions were noted simultaneously. Consecutively, post diagnosis onset of migraine headaches was noted in none of the 634 patients.

The correlation between migraine and dementia was observed in the DBL group. However, the strength of correlation can be debated as only 1 in 100 patients were considered to have migraine headaches before dementia onset [75]. Similarly, Lee et al. conducted a case-control study on 11,438 dementia patients. Diagnostic criteria were based off International Classification of Disease-10 (ICD-10F00). Patients aged 60> were considered for the study due to ethical research purposes. The results signified that the average duration from significance of migraine until dementia diagnosis was 58.6 months compared to 60.8 months in the control group. Respectively, the rate of occurrence for migraine diagnosis preliminary to dementia was higher in the cases (7.7%) as compared to the control (6.3%) group. Like other studies conducted, it was also seen that dementia diagnosis was greater in women than in men. It was observed that the risk of dementia was higher in patients that were diagnosed with migraine headaches after matching for age, sex, income, region of residence and past medical history. Women above the age of 70 showed the greatest association between migraine and dementia. It was concluded that dementia rates could possibly be decreased by controlling migraine headaches before onset of dementia symptoms [76].

In a meta-analysis between 1966 and 2004, migraine headaches were proven to be a risk factor for ischemic stroke [77]. White matter hyperintensities were seen to be more prevalent in patients diagnosed with migraine headaches as compared to the general population [78-81].

Various studies showed migraine to have a negative effect on cognitive skills including attention, verbal ability, memory and psychomotor ability [81-87]. On the other hand, certain studies proved no correlation between migraine and cognitive decline and thus contradicting the argument [81, 87-92, 103]. Another population-based study that was noted by Koen was significant of no difference in cognitive tests on 536 migraineurs [81, 103].

As seen in most studies, dementia and migraine can be allocated to CADASIL as an intermediating factor. The

thickening of arteries can cause migraines, leukoencephalopathy, small deep and subcortical infarcts and ultimately lead to dementia [104, 105]. Recurrent migraines can be seen in mitochondrial myopathies, encephalopathy, lactic acidosis and stroke like episodes. Mitochondrial disorders such as Leber's hereditary optic neuropathy, myoclonic epilepsy are also significant for migraine headaches [105, 106]. Research by Le Pira et al. [105] signified that migraineurs had a decrease in short- and long-term memory recall. The migraine groups self-reported problems with concentration, comprehension, and communication shortly after an onset of their migraine headaches. Signifying mild symptoms of dementia [105].

In a population-based study using data from the Nord-Trondelag Health Surveys conducted between the years 1995-1997 (HUNT2) and 2006-2008 (HUNT3) the relation between migraine and dementia was analyzed by Røttereng et al. In the study conducted years ago, Questionnaires consisting of more than 200 health-related items were presented to citizens of Nord-Trondelag County in Norway. Using the dementia registry, 1332 dementia patients were distinguished and identified. Diagnostic criteria for dementia were the same as national and international standards. After adjusting for age, gender, education, smoking, hospital anxiety and depression scale (HADS) and severe comorbid conditions, headaches were more persistent and more likely to be reported in HUNT2 from those who later on were associated with the Dementia Registry. This signified a direct and positive correlation between dementia and preceding headaches. It was also discussed that it was less likely for someone to report headaches that later were confirmed non-demented. In their other studies including 378 cases of dementia, patients with headaches proved to have higher risks for dementia onset [107, 108].

Multiple silent or sub-clinical lacunar strokes are amongst the findings in patients diagnosed with dementia. A hypothesis presented by Arnold Eggers, signified that a similar presence of silent cryptogenic strokes were seen in migraine patients. Thus, pointing out another relationship between the 2 diseases [109]. In a similar review article, the relationship between dementia and migraine was sought. The researchers deduced that migraines with or without aura can ultimately lead to cognitive decline. It was noted that the frequency of migraine headaches is also a contributing factor to onset of dementia. In some studies patients that signified migraine headaches had a higher chance of Alzheimer's disease and dementia. However confounding factors including non-migraine headaches such as cluster and TTH headaches were seen to be similarly causal in the dementia patients [110-112].

Conflict of Interest

The authors declare no conflicts of interest.

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