DEMENTIA AND GENETIC: A REVIEW

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Abstract

Dementia is a health concern worldwide, as there is currently no cure for this neurodegenerative disease. Many studies have been conducted to better understand the symptoms and causes of this disease. Dementia can be diagnosed in a person as early as 40 years of age, which has been a source of concern for everyone. Most of the population have a long-held belief that dementia would only affect the elderly. Genetic factors may have the potential to improve the accuracy by which specific causes of dementia can be diagnosed in clinical. A comprehensive review of the literature was conducted to gather credible and up-to-date information regarding this disease from previous studies. This review study will therefore aid in the understanding of different types of dementia, as well as the genetic factors that contribute to dementia.

Keywords: Dementia, Genetic, Neurodegerative disease, Alzheimer's

Introduction

According to the most recent data provided by the World Health Organization (WHO), dementia is the seventh major cause of death worldwide, placing it in the seventh place overall in terms of mortality. Elderly people are at an elevated risk of acquiring dementia, and this risk increases as the age of the individual increases (1). The diagnosis of dementia is growing more frequent among our ageing population, and it is anticipated that the number of persons diagnosed with the disease will increase in the years to come. In 2016, 50,000 people in Malaysia have been affected by this illness. It is shocking to learn that the majority of Malaysians consider Alzheimer's disease (AD) to be a natural part of the ageing process; as a result, they do not seek medical attention or diagnosis for it (2). In 2020, the Centers for Disease Control and Prevention (CDC) anticipated that Alzheimer's disease would afflict 5.8 million Americans. (3). After the age of 65, the number of patients doubles every five years. By 2060, the number could reach 14 million. Around the world, 75% of all dementia cases go undetected with the figure rising to 90% in low- and middle-income regions (4).

Dementia limits the capacity of an individual to recall, reason, or make judgements, thus, impairing their ability to perform daily chores (5). According to the CDC, this illness can be detected based on several signs and symptoms, such as being forgetful and forgetting the names of close family members, being disoriented in the neighbourhood, and using unusual terms to refer to familiar objects. Increased age, family history, ethnicity, poor heart conditions, and traumatic brain injuries are among the risk factors for dementia that are becoming more prevalent among the population (3). According to a previous study, the risk of moderate cognitive impairment among Malay people is twice as high as it is among people of other ethnic groups (6). Following a diagnosis, neuropsychiatric symptoms (NPS) such as aggression, depression, agitation, apathy, psychosis, and disinhibition are associated to the unrelenting progression of the disease (7). For patients suffering from dementia, a care plan is required in order to reduce risks and enhance outcomes.

Alzheimer's disease (AD)

Alzheimer's disease (AD) is a neurological illness characterised by the progressive degeneration of brain cells over time, which is commonly diagnosed. Some of the signs and symptoms of dementia include a deterioration in mental capacity as well as a reduction in the degree of independence in performing the activities of daily living (8). It is believed that AD is responsible for around 80% of all diagnoses of dementia, making it the most frequent cause of dementia in every country in the world (9). It is a degenerative neurological condition that is both irreversible and severe, resulting in a substantial social and economic burden.

Neurofibrillary tangles of hyperphosphorylated tau and amyloid plaque deposition in the brain are the two characteristic pathologies of this neurodegenerative disease process commonly observed in patients with AD (10). According to Breijyeh and Karaman (8), accumulation in the areas of the brain that are the most impaired,

specifically the medial temporal lobe and the neocortical structures, could be a factor in the development of AD. This accumulation could disrupt communication between nerve cells, as well as disrupt processes that cells require in order to survive.

Lewy body dementia

After AD, Lewy body dementia (LBD) is the prevalent type of progressive dementia (11). LBD is more commonly diagnosed in men than women. Post-mortem studies showed that the underlying pathology was different between men and women (12). LBD is characterised by a progressive deterioration of mental functions. People suffering from LBD may have visual hallucinations, as well as changes in their level of attentiveness and concentration.

Lewy bodies are clumps of protein that form in the nerve cells in the brain that are important for thinking, remembering, and motor control. LBD would be caused by the accumulation of -synuclein in neurons in the cortex. Distributions of α-synuclein and tau pathology can be associated with the phenotypic expression of LBD. LBD is a highly likely clinical diagnosis when the number of -synuclein pathologies is higher than the number of tau pathologies (13, 14). Other repercussions might include the signs and symptoms of Parkinson's disease (PD), such as stiff muscles, slow movement, difficulty walking, and tremors. Since LBD and PD share the same base features, there is a '1-year rule' to differentiate these diseases. Patients will be diagnosed with LBD at least a year after PD (15).

Frontotemporal dementia

Frontotemporal dementia (FTD) is used to refer to a set of neurodegenerative diseases that are characterised by impairments in behaviour, executive function, language, and mental processes (16). It is common among those under the age of 65, and also most underdiagnosed diseases, because the symptoms usually coincide with symptoms of mental illnesses (17). The most impacted are in the frontal and temporal lobes by becoming significantly shrunken (18). The frontal lobe is especially important for cognitive functions and voluntary movement, or activity control, while the temporal lobe is responsible for vision, language, and emotion.

Behavioural variant frontotemporal dementia (Bv-FTD) and primary progressive dementia (PPD) are the two clinical subtypes of frontotemporal dementia. As both disease progress, their symptoms might become more similar, as an originally focal degeneration becomes more diffused and expands to impact significant parts of the frontal and temporal lobes, respectively. Global cognitive decline and motor deficits would occur in patients over time, including parkinsonism and motor neuron disease in a subset of patients. Patients in the late stages have difficulties swallowing, moving, and eating. Death usually occurs approximately eight years after the onset of symptoms and is mainly caused by pneumonia or infections (19).

Vascular dementia

Vascular dementia is the 2nd most common kind of dementia after AD with a variable presentation and unexpected disease course (20, 21). Patients suffering from vascular dementia frequently struggle with judgement and memory as a result of decreased blood supply to the brain, which would subsequently result in brain damage. The risk of vascular dementia doubles every five years with increasing age (22).

Vascular dementia is most frequently caused by blood artery blockage, or injury, which results in brain tissue death, or haemorrhage. Vascular dementia can also occur as a result of other illnesses that damage blood vessels and impair circulation, depriving the brain of necessary oxygen and nutrients. Hyperlipidaemia, hypertension, diabetes, and tobacco use can cause vascular dementia. Due to similar symptoms of mixed dementia syndrome, vascular dementia is difficult to diagnose (21).

Mixed dementia

Mixed dementia is a disorder in which the brain has alterations consistent with more than one type of concurrent dementia. People with Alzheimer's disease always have other forms of dementia as well. Plaques and tangles are the most prevalent indicators of Alzheimer's disease, whereas blood vessel alterations are the most prevalent indicator of vascular dementia. To cause dementia, Serrano-Pozo and Growdon (23) reported that AD is pathologically defined by the presence of amyloid plaques and neurofibrillary tangles (NFTs) in sufficient numbers and distribution. Previous studies have established that a combination of AD and cerebrovascular disease pathologies, as well as LBD and hippocampal sclerosis is the most commonly diagnosed in the elderly. Over the age of 85, the probability of having mixed dementia increases (24).

Genetic factors related to dementia

The risk of developing late-onset Alzheimer's disease is mostly influenced by the apolipoprotein E4 (ApoE4) gene. ApoE4 acts as a template for the formation of a protein that is responsible for transporting cholesterol throughout the circulatory system of the body (25). Everyone obtains one variation (alleles) of the ApoE gene from each of their parents: e2, e3, or e4. This results in six pairs which are e4/e4, e3/e3, e2/e2, e2/e4, e2/e3, and e3/e4 (26).

ApoE3, ApoE4, and ApoE2 genes relate to an increased risk of Alzheimer's disease whereas apolipoprotein E2 (ApoE2) acts as a preventive factor against the disease. Individuals with the ApoE4 variant have a significantly increased chance of being affected by Alzheimer's disease compared to those with the e3 type. However, possessing the e4 variant of the gene does not guarantee that a person would get Alzheimer's disease (27). Previous research have demonstrated that those who inherited one copy of the e4 are three times more likely to develop Alzheimer's

disease than those who received two copies of the e3 form. Individuals with two copies of the e4 type, on the other hand, have an eight- to twelvefold increase in developing Alzheimer's disease (28).

The bulk of Alzheimer's cases are due to mutations in any of these three genes, which account for fewer than 1% of cases (29). Human mutations can be caused by viral infection, exposure to ionising radiation, exposure to mutagens, or errors in DNA copying during cell division. As a result of these changes, the amyloid precursor protein (APP) and the presenilin 1 and 2 proteins may be disrupted. Individuals who inherited an Alzheimer's disease mutation in one of these genes will surely develop the condition (30). The majority of those with Alzheimer's disease have the late onset at age 65 and also as early as the age of 30.

If a person has Down syndrome, their chance of developing Alzheimer's disease in their early years is significantly raised. Alzheimer's disease is a condition that affects many people who have Down syndrome as they get older. The symptoms can be detected as early as in their 50s or 60s (31). Researchers believe that an extra copy of chromosome 21 in Down syndrome patients results in an overexpression of the amyloid precursor protein gene (32, 33).

A significant history of the disease in the family can be found in approximately one third of FTD patients. FTD is the most common form of dementia under the age of 60, with an estimated lifetime risk of 1 in 742 people having the condition (34). Alzheimer's disease is not contagious and can develop in people without a prior history of the illness in their family. Individuals who do not have a first-degree relationship with Alzheimer's patients have a lower risk of developing the condition, whereas those with a first-degree relationship have a higher risk of getting the disease (35). Previous research indicates that siblings of individuals diagnosed with LBD are at a greater risk of developing LBD than siblings of individuals diagnosed with AD. In addition to this, people with LBD are more likely to have a history in their family of dementia or Parkinson's disease compared to patients in the control group (36).

Conclusion

Dementia is seen as a public health emergency around the world. Dementia syndromes are widespread among elderly individuals, which are anticipated to develop poor quality of life in future. It is characterised by the loss of cognitive, psychological, and physical abilities. Currently, there is no cure for dementia and medications are only beneficial in slowing the advancement of the disease in some patients. The aetiology of dementia can be identified by thorough medical history, cognitive assessment, physical examination, laboratory testing, neuroimaging and biomarkers which includes cerebrospinal fluid (CSF). The difficulties in finding clinically meaningful biomarkers of disease progression indicates that other factors need to be researched in the future.

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Competing Interests

The authors declare that they have no competing interests.

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