The Relationship Between the Three Genes of Apolipoprotein E and the Hippocampus and Interference with Alzheimer's Disease

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Abstract. Glycoproteins in the Apolipoprotein E (APOE) class have a role in controlling lipid metabolism. In astrocytes, microglia, vascular wall cells, and choroid plexus cells of the central nervous system, it is abundantly expressed. According to the rapid advancement of contemporary medicine, numerous investigations have demonstrated the existence of ApoE in chylomicron (CM), very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and certain high-density lipoprotein (HDL). ApoE has also been demonstrated to have a substantial impact on Alzheimer's disease (AD). To enhance the investigation of innovative medications and give researchers a theoretical foundation, research on ApoE is required in this area. Because damage to the hippocampus is a significant concern for the population in Alzheimer's research, we need to study the effects of ApoE on the hippocampus. This paper will discuss the relationship between age and sex of hippocampal atrophy after the ApoE gene has caused AD. The paper through a method of literature review and the analysis of some clinical cases explores the impact of the ApoE gene on health, followed by a comparison of the disease state before and after, as well as the clinical pattern of hippocampal atrophy, including a description of clinical symptoms. The paper finds that ApoE significantly impacts AD and that the hippocampus is significantly atrophied after the onset of Alzheimer's disease.

Keywords: APOE 4, APOE 2, hippocampus, Alzheimer’s disease

1. Introduction
Alzheimer's disease (AD) is a slowly developing, degenerative neurological condition with a sneaky onset. People over the age of 70 are most frequently affected by the condition. The prevalence is higher in post-menopausal women than in men in the 40–60 age group [1]. Clusters of misfolded -amyloid (Aβ) [2] and Tau proteins are among the more well-known characteristics of AD cases and are often always present in the brain [3]. The blood-brain barrier (BBB) changes are also emerging as a marker for early neurodegenerative disease, which raises the possibility that Aβ and Tau may not be the only factors at play [4].

The hippocampus, which is the name given to a region of the brain located in the temporal lobe and has two hippocampi, one in each of the left and right hemispheres, is shown to have suffered the most extensive damage in the AD study. It functions in memory and spatial orientation and is a component
of the limbic system, which makes up the brain. Thus, memory loss and loss of directional sense are the main symptoms of AD, and patients also create false memories as a result [5].

The APOE gene is located on the long arm of three regions of chromosome 19q13.32 [6] and three introns. 3,611bp of the gene, with four exons and 1,180nt of mRNA, encodes a protein consisting of 299 amino acid residues. ApoE2, ApoE3 and ApoE4 [7], of which ApoFA inhibits the function of ApoE2 and ApoE3 and reduces the stability of neuronal membranes, leading to tangling and death of neuronal fibres. ApoE3 is the wild type [8]. ApoE3 is the wild type and accounts for about 70.8% of the natural population. ApoE2 is the variant. It is a long-lived gene. ApoE4 is also a variant. It is associated with a high prevalence of Alzheimer’s disease and hurts the recovery of function from various traumatic brain injuries. The long-lived gene E2 corresponds to the genotypes ε2/ε2 and ε2/ε3 and accounts for 7.8% of humans [9]. Individuals with this genotype are relatively less susceptible to AD, but their lipids show high triglycerides, low Lactate dehydrogenase C(LDH-C) and uncertain high-density lipoprotein (HDL). The wild-type gene E3 corresponds to the genotypes ε3/ε3 and ε2/ε4, which account for 70.8% of humans, and these are common genotypes. The risk type gene E4 corresponds to the genotypes ε3/ε4 and ε4/ε4 and accounts for 21.4% of humans. Individuals with this genotype are susceptible to AD, and their blood lipids are expressed as not high triglycerides, high LDH-C and low HDL.

According to research, APOE 4 is the single most significant genetic risk factor for cognitive decline and AD. The substantial body of evidence demonstrates that the APOE4 gene is connected to the BBB and affects the volume of the hippocampus [10]. Although there is no pathogenic link between Alzheimer’s disease and hippocampus atrophy, there is a connection between the two. Many patients with a clinical diagnosis of Alzheimer’s disease or cognitive impairment had MRI pictures showing hippocampal shrinkage, according to an examination of several medical imaging. Numerous studies have demonstrated that modulation of APOE ε4 has an impact on brain structure and function, cognition, and behavior in healthy people, notably in the hippocampus, a crucial area linked to AD pathology [11].

In this paper, we will discuss the relationship between age and sex of hippocampal atrophy after the ApoE gene has caused AD. The effect of the APOE ε4 allele on cognitive performance, hippocampal structural morphology, and in particular, functional characteristics of AD patients, is still unknown. The paper through a method of literature review and the analysis of some clinical cases explores the impact of the ApoE gene on health, followed by a comparison of the disease state before and after, as well as the clinical pattern of hippocampal atrophy, including a description of clinical symptoms.

The findings presented in this paper is significant because it shows that APOE is a substantial risk factor for late-onset AD that manifests after the age of 65, but APOE ε2 protects against AD and APOE*ε4 increases the probability of acquiring AD. In contrast, the main symptom of AD is a memory loss that is clinically represented by hippocampal destruction [12]. Because of this phenomena, there is a huge need for in-depth research to lessen the influence of APOE on this illness. The APOE gene impacts not only Alzheimer's disease but also other illnesses.

2. Methods
The author systematically searched four English databases (PubMed, Open access Library, springer and SCI Pub) and two Chinese database (CNIK and Wan fang) for literature on the effects of APOE genes on hippocampal volume and Alzheimer’s disease, using a combination search strategy with terms such as "hippocampus", "hippocampal volume", "ApoE 2", "ApoE 3", "ApoE 4", "Apolipoprotein E", "Alzheimer's disease", "beta-amyloid plaques", "tau protein", "TDP43 protein", "ApoE gene", "pathology", "genetics", "experiment", and "risk factor". The database was searched from the time of creation until January 1, 2017, with no limitations on language. The reference lists of the retrieved publications were carefully reviewed, and we made an effort to get more information by getting in touch with the authors. We looked for extra relevant information in the reference lists of articles. All pertinent papers published in English or Chinese were included in the screening of about 3050 abstracts. The final reference list was created based on its applicability to the subjects discussed in this review. In the case of numerous investigations, the same data, including the most recent papers, were available as a narrative review.
Much literature was read for the data extraction part, and some relatively complete data were obtained by requesting data from relevant experienced doctors. Some collation and analysis of this data will also be done in this paper, as many of the data are relatively old, and it is cumbersome to contact the authors of the experimental papers, so this part of the literature was removed from the reading when sifting through the literature. The following information was screened independently from each study: the year of publication within five years, the feasibility of the argument in the paper at this stage, the relevance to the thesis of the paper, the age group and gender of the Alzheimer's data collection, the direction and setting of the study, the description of the patient's underlying disease and the total number of data sources. The appropriate medical staff (neurologists, laboratory physicians, and imaging doctors) were subsequently interviewed as part of an essential evaluation to validate the viability and reliability of the data. Emails were sent to the original authors requesting any missing raw data.

3. Results

3.1. The relationship between APOE 4 and hippocampal volume

The extracellular Aβ protein buildup and intracellular neurofibrillary tangle formation caused by hyperphosphorylated Tau proteins are the two primary pathogenic characteristics of AD, respectively [13]. The aetiology and pathophysiology, however, remain unknown. Numerous genome-wide analyses have demonstrated that the most reliable genetic risk factor for AD is the APOE4 allele, which is linked to the disease. In May 2020, Montagne A et al. made the discovery that the APOE gene causes BBB. The results showed that individuals with the apoe4 gene variation have an elevated risk of Alzheimer's disease. According to the study, this variation is linked to BBB deficiencies and ensuing cognitive deterioration, which was published in Nature [12]. In this study, Zlokovic's team enlisted 245 people and used dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) methods to assess each volunteer's blood-brain barrier permeability. They as a result came to numerous conclusions. First, compared to cognitively normal APOE3 pure volunteers (ε3/ε3), there was a greater disruption of the blood-brain barrier in the hippocampus (HC) and parahippocampal gyrus (PHG) in APOE4 carriers (ε3/ε4 or ε4/ε4). Furthermore, there were no differences between this rise and the levels of phosphorylated tau and a-amyloid in the cerebrospinal fluid (CSF) [14].

In contrast, even in APOE3 carriers with cognitive impairment, there were few changes to the blood-brain barrier in the hippocampus and parahippocampal gyrus. Second, they also observed a phenomenon in which the volume of the hippocampus and parahippocampal gyrus in APOE4 carriers, too, shrank in response to cognitive impairment, but APOE3 carriers did not show such changes. Impairment of the blood-brain barrier in the hippocampus and parahippocampal gyrus in APOE4 carriers remained highly correlated with cognitive impairment [15], but no such correlation was found in APOE3 parts. This was true even after controlling for the confounding factors of age, sex, literacy, cerebrospinal fluid levels of beta-amyloid and phosphorylated tau protein, and volume of the hippocampus and parahippocampal gyrus [16]. Third, they found that blood-brain barrier impairment preceded brain atrophy and was not associated with systemic vascular risk factors. These results support the hypothesis that the APOE4 gene pair is involved in the loss of hippocampus volume. One of the main clinical manifestations of early AD [17] and an early indicator of cognitive impairment in humans is BBB disruption. The APOE4 variant is a major susceptibility gene for AD, causing accelerated BBB destruction and degeneration of pericapillary cells in the brain, thereby maintaining the integrity of the BBB, even though the relationship between the genetic effects of APOE4 on the cerebral vasculature and AD is unclear [18].

3.2. The relationship between hippocampal volume and Alzheimer's disease

Current medical knowledge indicates that AD is a neurodegenerative illness that worsens over time and for which there is no cure. Age spots and neurofibrillary tangles grow in AD first, then there is neurodegeneration, which causes cognitive impairment and eventually death. The degenerative alterations in AD typically take place several years before the disease manifests. As a biomarker of
neurodegeneration, decreased hippocampus volume is present. As a result, utilizing medical imaging, we can make assumptions about the connection between cognitive decline, Alzheimer's disease, and decreased hippocampus volume. A biomarker of AD is thought to be hypometabolism in the temporoparietal area. Glucose uptake is a function of astrocytes rather than neurons [19].

In the Walhovd et al. study, a sample of 1181 people (aged 4-95; mean age at visit: 39.7; SD: 26.9 years) underwent 2690 brain scans, including APOE variants about hippocampus volume and its changes, and were then monitored for up to 11 years. In October 2020, this experimental research was released in Neurology Genetics. They came to the conclusion that segregation of AD-PGS and APOE ε4 dramatically decreased hippocampus volume. Hippocampal volume was expected to decrease by -36.4 mm³ when 1 sample SD was added to AD-PGS (confidence interval [CI]: -71.8, -1.04), while it increased by 107.0 mm³ when carrying the ε4 allele(s) (CI: -182.0, -31.5). The interplay of age and genetic risk on volume change was inconsistently seen, and the offsetting effects of AD-PGS and APOE ε4 were seen in the developing hippocampus. This study also demonstrates that hippocampus shrinkage affects people of all ages and is not just a problem in the elderly. As a result, Alzheimer's disease has a long illness cycle and is not just a condition of the old [20].

In this regard, the authors also acquired a sample of instances, with a total of 12 elderly cases (aged 59 years or older, four males and eight females, with case information taken within six months Table 1). Due to the restricted resources, no blood samples were obtained in these instances, therefore the APOE4 gene was not identified. However, we were still able to see the hippocampus volume atrophy through their MRIs (Figure 1 and 2). All of the cases were AD patients who had clinically evident medical diagnoses as well as varied degrees of cognitive impairment or more serious illnesses. Both unilateral and bilateral hippocampus atrophy were present in some cases. It was nevertheless able to analyze the connection between AD and hippocampus atrophy in these cases even if the patients had varying degrees of atrophy. Permission was obtained from the patient for all the above data. For some reason, the latter three patients only provided basic information and did not provide medical images.

![Figure 1. These are the medical images of the first 9 patients (coronal).](image-url)
Figure 2. These are the medical images of the first 9 patients (transverse).

Table 1. This is the basic information of 12 patients together with their clinical diagnosis and medical imaging diagnosis.

<table>
<thead>
<tr>
<th>Age(years)</th>
<th>Diagnostic Medical Imaging</th>
<th>Clinical Medical Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>Bilateral hippocampal volume atrophy</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>76</td>
<td>Bilateral hippocampal volume atrophy</td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>74</td>
<td>Bilateral hippocampal volume atrophy</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>85</td>
<td>Bilateral hippocampal volume atrophy</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>76</td>
<td>Bilateral hippocampal volume atrophy</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>69</td>
<td>Bilateral hippocampal volume atrophy</td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>83</td>
<td>Bilateral hippocampal volume atrophy</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>77</td>
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<td>Alzheimer’s disease</td>
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<tr>
<td>76</td>
<td>Bilateral hippocampal volume atrophy</td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>51</td>
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</tr>
<tr>
<td>71</td>
<td>Bilateral hippocampal volume atrophy</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>62</td>
<td>Atrophy of the right hippocampal volume</td>
<td>Alzheimer’s disease</td>
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4. Discussion

ApoE is involved in the conversion and metabolism of lipoproteins, and its genes regulate many biological functions. There are three main known alleles of ApoE, ε2, ε3 and ε4, which encode the three main ApoE heterozygotes, E2, E3 and E4. Thus in mixed combinations, there are six different phenotypes: three pure and three hybrids. In some studies of AD, we have found that this gene interferes with Alzheimer’s disease and triggers the disease and that the ApoE4 gene increases the likelihood of Alzheimer’s disease in people.

The significance of the research in this paper is that APOE is a significant risk factor for late-onset AD after the age of 65, where APOE ε2 is protective against AD and APOE*ε4 enhances the risk of developing AD. In contrast, damage to the hippocampus is the primary condition of AD, clinically manifested by a decline in memory [21]. For such a phenomenon, there is a great need for extensive research to reduce the impact of APOE on this disease, and the same gene for APOE affects not only Alzheimer’s but also other diseases.

The genotype of APOE has a long-term impact on the health of the body, not only in terms of diet, but also in terms of maintaining good health and preventing a range of major diseases and, in the event of disease, in determining the unique individualised treatment.
This paper focuses on the six congeners that arise from the three alleles of APOE, ε2, ε3 and ε4, and how they affect Alzheimer’s disease in people differently in different situations. In this paper, the study has implications for future research. Future attention could be paid to deeper molecular mechanisms, as ApoE studies are based on molecules of genes in the blood. This issue is discussed so that genes that can be detected can be targeted to study the mechanisms that should cause the disease in the future. New drugs can be developed with causative mechanisms as a way to reduce the impact of the disease on the human body and also as a way to prevent the disease before it develops.

5. Conclusion
In conclusion, APOE was a significant risk factor for late-onset AD after age 65, with APOE ε2 being protective against AD and APOE ε4 enhancing the risk of developing AD. The proportion of APOE genotypes carried also affects the probability of developing AD. For example, carrying one APOE ε4 increases the risk of developing AD by 3-4 times, while carrying two APOE ε4s increases the risk by 9-15 times [22]. Numerous research have revealed that APOE controls the levels of beta-amyloid plaques, tau protein, and TDP43 protein expression in AD patients’ brains and influences healthy brain function.

In this research, although much literature has been searched and valuable information from the literature within the last five years has been summarised and analysed, there are still many shortcomings. Firstly, there is not a lot of operational data used in this paper; most of the data resources are derived from the literature, and the actual data may vary but not be well perceived. The second is that the studies are not comprehensive enough, and much of the literature does not show an apparent causal relationship, as the logical chain is missing and does not go into specifics. The third is the lack of image processing and insufficient sample size. Many cases require medical image processing, which is rather vague, and only a relatively small sample size can be obtained. Future attention could be paid to deeper molecular mechanisms, as ApoE studies are based on molecules of genes in the blood. This issue is discussed so that genes that can be detected can be targeted to study the mechanisms that should cause the disease in the future. New drugs can be developed with causative mechanisms as a way to reduce the impact of the disease on the human body and also as a way to prevent the disease before it develops.

References


