International Journal of Dermatology, Venereology and Leprosy Sciences

E-ISSN: 2664-942X
P-ISSN: 2664-9411
www.dermatologypaper.com
Derma 2025; 8(1): 06-12
Received: 08-11-2024
Accepted: 14-12-2024

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The link between serum beta-amyloid and serum apolipoprotein E4 in psoriasis and cognitive impairment

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DOI: https://www.doi.org/10.33545/26649411.2025.v8.i1a.218

Abstract
Multiple forms of the chronic skin disease psoriasis can manifest over a person's lifetime, including plaque, flexural, guttate, pustular, and erythrodermic. Multiple factors, including immunology, genetics, and the environment, contribute to the development of psoriasis. As an important societal concern, psoriasis can negatively impact patients' quality of life by causing physical impairment, making it impossible for them to work, and so on. An inflammatory skin condition known as psoriasis triggers immune pathways that involve dendritic cells, NK cells, macrophage cells, and an inflammatory mediator. The pathophysiology of Alzheimer's disease (AD) dementia is characterized by two proteins aggregations: beta-amyloid into plaques and phosphorylated tau into neurofibrillary tangles. According to popular belief, the abnormal buildup of amyloid protein is seen as an early initiating event in the AD cascade, and the spread of Tau into the neocortex and medial temporal lobe happens later on, closer to the onset of clinical symptoms of dementia, in contrast to this. The renowned genetic risk factor for Alzheimer's disease, apolipoprotein E4 (APOE4), may have an effect on the cognitive impairment linked to Parkinson's disease (PD).
This review article aims to determine the link between serum beta-amyloid and serum Apolipoprotein E4 in psoriasis and cognitive impairment.

Keywords: Psoriasis, chronic skin disease, inflammatory skin condition, plaque psoriasis

Introduction

Psoriasis vulgaris

Psoriasis is a chronic, non-contagious, multisystem, immune-mediated skin disorder. Psoriasis is a multifactorial condition which is caused by interaction between genetic susceptibility and environmental triggers. Skin lesions on the scalp, elbows, knees, lumbosacral regions, intergluteal clefts, and glans penis are the most common symptoms of psoriasis. Psoriasis can also manifest in the joints, affecting as many as 30% of patients. Flares caused by environmental or systemic factors, such as infections or stressful life events, cause it to wax and wane. The detrimental impacts of psoriasis on patients' quality of life (QOL) have been extensively documented, and the disease is known to be associated with a number of comorbidities, such as polycystic ovary syndrome (PCOS), metabolic syndrome, cardiovascular disease, and mental health issues [1].

Dermatologists first identified psoriasis as a relapsing and remitting condition 100 years ago. Treatment resulted in only a temporary remission, not a cure. However, treating psoriasis as a standalone skin condition using this method has become obsolete in recent years. Current thinking holds that psoriasis is an inflammatory disorder mediated by the immune system that affects the entire body and often comes with other health problems, including psoriatic arthritis, cardiovascular disease, and mental health issues [2].

According to previous research, five different kinds of psoriasis can manifest in patients. There are various types of psoriasis, such as guttate (droplet) or eruptive psoriasis, plaque psoriasis, pustular psoriasis, and the extremely rare and severe generalized pustular psoriasis. Other forms of psoriasis include palmoplantar pustulosis, erythrodermic psoriasis, and psoriasis vulgaris, which are another name for plaque psoriasis [3].

Psoriasis is typically diagnosed based on clinical findings; however, skin biopsies are rarely performed in this context. For patients with extensive psoriasis, the PASI score is commonly used to measure the severity of infiltration, scaling, thickness, lesion extent, and erythema. While infections can set off psoriasis, the skin condition itself is not infectious. Because psoriatic arthritis can develop in up to 30% of psoriasis patients, dermatologists should ask more detailed questions about the patient's medical history [4].

Everyone now acknowledges that the immune system plays a role in psoriasis. Psoriasis genome-wide searches have revealed a link between heredity and immunity, with the majority of the genes found to be involved with the immune system. Psoriatic skin lesions may be caused by the immune system's dysregulated interactions with resident cutaneous cell types. Insight into the immunopathogenesis of psoriasis has resulted in the creation of multiple targeted therapies. As part of the intricate feedback loops involved in psoriasis, the cutaneous nervous system, neutrophilic granulocytes, keratinocytes, and vascular endothelial cells are all involved. A critical function in disease mediation is performed by dendritic cells and T-cells. Several new targeted therapies have been developed in response to the increasing interest in the interleukin-23/Th17 axis in psoriasis. It is known that Th17 cells express interleukin 17 among the subsets of T-lymphocytes. Inflammatory diseases like psoriasis rely heavily on classical Th17 cells, but these cells are different. The interleukin-23/Th17 axis pathway and the TNFα pathway impact nearly every type of skin cell, displaying intricate dysregulation. In particular, this is the case for cells that play a role in the proliferation of epidermal keratinocytes and the production of cytokines [5].

Pathophysiology in psoriasis variants

The TNFα-IL23-Th17 axis plays a pivotal role in T cell-mediated plaque psoriasis, whereas the innate immune system appears to play a more significant role in pustular psoriasis variants. In pustular psoriasis, IL-1β and IL-36 transcripts are expressed at a higher level than in psoriasis vulgaris. Because IL-17 signaling is also involved in generalized pustular psoriasis, anti-IL-17 therapy may help alleviate symptoms in people with this condition [6].

It is believed that streptococcal super antigens cause guttate psoriasis by triggering the skin's T cell expansion. The majority of streptococcal M proteins and K17 proteins share a very similar sequence. Patients who carry the HLA-C*06:02 allele may be affected by molecular mimicry, as K17 and M6 peptides were able to elicit CD8+ T cell IFN-γ responses in these patients [7].

The presence of inflammatory markers in psoriatic skin lesions is corroborated by the elevated expression of TNF-α, NFκB, IL-6, and IL-8 in the nails of individuals with nail psoriasis and PsA. In PsA, clonal expansions of CD8+ T cells are observed in synovial tissue, and the expression of pro-inflammatory cytokines such as IL-1, IFN-γ, and TNFα is elevated. In PsA, bone destruction is mediated via IL-17A signalling and pro-inflammatory cytokines, which induce the receptor activator of NFκB ligand (RANKL), and in turn, activates osteoclasts [8].

Serum Beta-Amyloid

Structure of the amyloid beta peptide

It is the much larger precursor APP from which the Aβ peptides are separated. A crucial protein present in numerous tissues, particularly in the synapses between neurons, amyloid-β (APP) has a significant impact on the progression of Alzheimer's disease (AD). The amino terminus of APP is shorter and located in the cytoplasm, while the N-terminus is extracellularly glycosylated. APP also contains a single domain that spans the cell membrane. A bigger family of genes exists in humans, and this is just one member of it [9].

Aβ monomer

As Aβ monomers combine, various assemblies can be created, including oligomers, protofibrils, and amyloid fibrils. Differences between amyloid oligomers and amyloid fibrils include the former's solubility and the latter's ability to aggregate into larger, insoluble structures that can spread throughout the brain. The primary amino acid sequence for Aβ was first identified in amyloid plaques and extracellular deposits in 1984. Aβ comprises peptides with sizes ranging from 37 to 49 residues. It is common to find Aβ-primarily composed plaques in the neocortex of the brains of Alzheimer's disease patients [10].

It is generally believed that Aβ cannot be crystallized using conventional methods because it is fundamentally unstructured. Consequently, a lot of studies aim to find the best conditions for stabilizing Aβ peptides. Using X-ray crystallography, molecular dynamic (MD) techniques, and nuclear magnetic resonance (NMR) spectroscopy, the three-dimensional solution structure of various Aβ peptide fragments was ascertained. Molecular dynamics and nuclear magnetic resonance (NMR) provide the majority of the structural information regarding Aβ (Figure 1) [11].

Serum Apolipoprotein E4 (APOE)

APOE and neuronal signalling

Also, APOE is involved in lipid trafficking from the periphery to the central nervous system and has a significant impact on neuronal signaling and the tripartite synapse (presynapse, postsynapse, and astrocytes). The efficacy of reelin at the APOE receptor 2 (APOER2) is one of the APOE-mediated neuronal signaling pathways that has been meticulously investigated. Neuronal migration, dendritic spine formation, and synaptic plasticity are all dependent on reelin binding. Reelin activates cystolic receptor disabled-1 (Dab1) and phosphorylates NMDA receptors; this leads to calcium influx and long-term potentiation (LTP). Because it encourages cellular uptake of APOER2, APOE4 is harmful to this process, in contrast to APOE2 and APOE3. This limits reelin binding, thereby causing a decrease in synaptic plasticity [13].

The entorhinal cortex (EC), the region initially impacted by the pathology of Alzheimer's disease (AD), is particularly vulnerable to the decline in reelin levels that occurs with age. Although these studies support the idea that APOE4 reduces neuronal signaling, there is some controversy surrounding the results that demonstrate early hippocampal neuronal hyperactivity in transgenic AD mice and individuals at risk for AD. Previous research has demonstrated that this rise in brain activity promotes the secretion of both amyloid and τ, which could hasten the onset of AD-related pathology. In later stages of the disease, neurodegeneration and hypoactivity may result from the cumulative effects of APOE4 on hyperactivity and pathology [14].

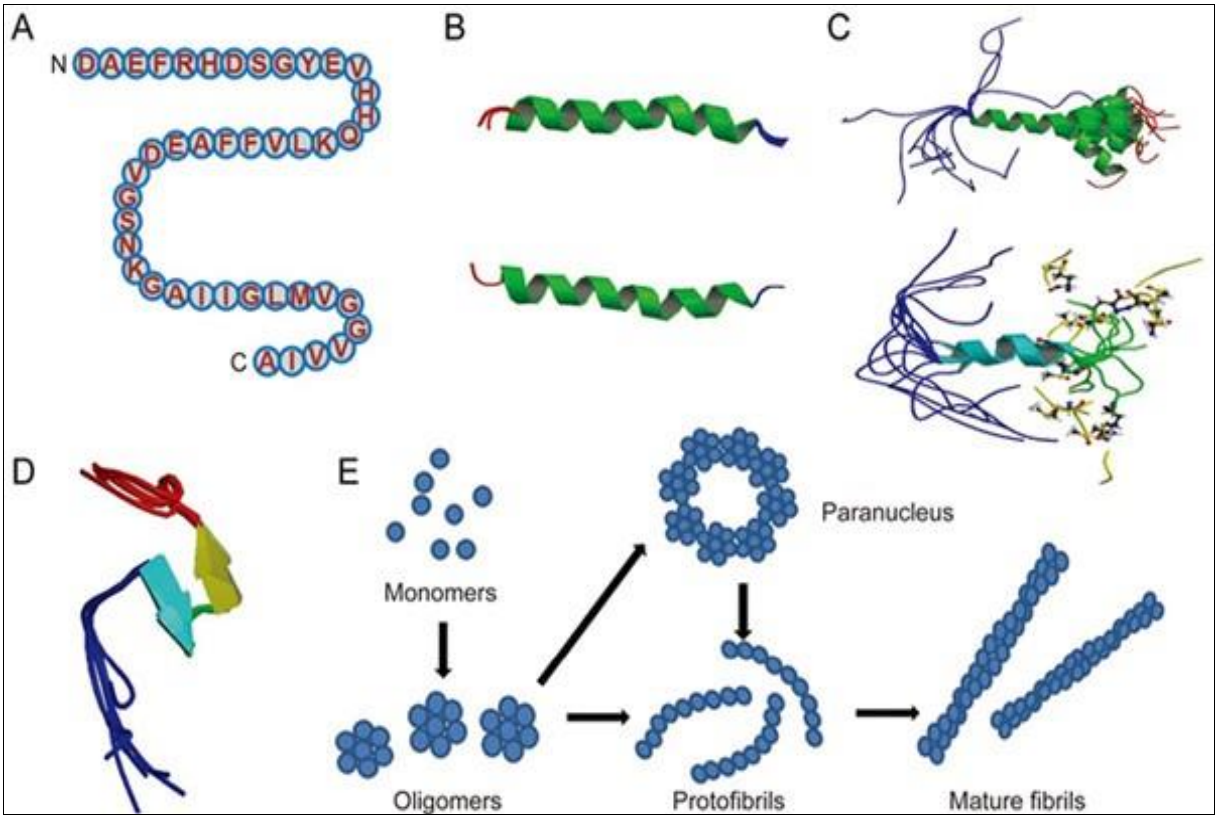

Fig 1: Structures of Aβ monomer, fibril and oligomers. (A) The primary amino acid sequence of the 42 amino acid Aβ isoform Aβ42. Aβ encompasses a group of peptides ranging in size from 37-49 residues. (B) The structure of amyloid beta peptide (1-28) (C) Solution structure of amyloid beta peptide (1-40), in which the C-terminal two-thirds of the peptide form an alpha-helix conformation between residues 15 and 36 with a kink or hinge at 25-27 in aqueous sodium dodecyl sulfate (SDS) micelles with a bend centered at residue 12. (D) Amyloid beta peptide (10-35) forms a collapsed coil structure (PDB code: 1HZ3). (E) Proposed pathway for the conversion of amyloid beta monomers to higher order oligomers, protofibrils and fibrils [12]

Recent research indicates that APOE4 also affects the presynaptic release of vesicles and glutamate, even though the majority of studies examining APOE4's effects on neuronal signaling have focused on the post-synaptic region. An increase in vesicular glutamate transporter 1 is a compensatory mechanism for APOE4 neurons' inability to convert glutamine to glutamate. Whether this has an immediate effect on glutamate synthesis and release in living things is yet unknown. The fact that reelin signaling via presynaptic APOER2 increases vesicle fusion to the membrane was previously known, though. Unanswered questions about the effects of various APOE isoforms on the presynapse could inform therapeutic and research directions moving forward [15].

Signaling those results in synaptic pruning, synaptic transmission, and glial transmission is carried out by astrocytes, the primary APOE source in the brain. In all likelihood, the APOE4 isoform restricts pruning via various phagocytic receptors like MEGF10, MERTK, AXL, INTEGRIN, α5β5, and LDL receptor-related protein 1 (LRP1). However, there hasn't been a lot of research on these mechanisms. Because healthy synapses rely on regular turnover, or pruning, this is significant. On the flip side, APOE2 keeps synapses free of old ones and speeds up the rate at which astrocytes phagocytose them. To summarize, APOE4 seems to have an effect on phagocytosis and glial activation, which could cause an influx of inflammatory cells and senescent cells in the brain of AD patients. Like the pruning mechanism, this improvement in glial activation is probably mediated by LRP1. All things considered, these studies point to the importance of APOE in controlling neuronal signaling and the detrimental effects of the APOE4 isoform on these signaling pathways [16].

APOE and β-amyloid hypothesis

According to reports, the binding of the other isoforms with Aβ is not as aggressive as that of APOE4, although the formation of APOE/AỤ complexes can affect senile plaque formation, AỤ clearance, and aggregation. APOE is essential for amyloid β (AỤ) metabolism. The Aβ load in the brain interstitial fluid is nearly two and four times higher, respectively, in an Alzheimer's disease mouse model that overexpresses human APOE4 isoforms (PDAPP/TRE) compared to mice that express APOE2 and APOE3, respectively. There is a positive correlation between the rate of clearance and the increased deposition of Aβ. The seeding stage of amyloid development is associated with elevated astrocytic apoE4 expression, which, according to recent evidence, increases amyloid deposition [17].

Moreover, APOE4 has the potential to influence Aɣ clearance in the brain by either interacting with Aɣ directly or by competing with other proteins for the same clearance pathway. The total rate of Aβ clearance is decreased when the two proteins use the identical pathway. Both Aβ and APOE4 pose challenges to the LRP1-dependent cellular uptake pathway in astrocytes. Within cells, LRP1 is involved in Aβ uptake and degradation through pathways involving phosphoinositide 3-kinase (PI3K) and extracellular signal-regulated kinase (ERK), as well as by modifying cytoskeletal enzymes such as MMP2 and MMP9 [18].

The overall increase in Aβ load is contributed to by APOE4, as it inhibits LRP1/Aβ binding competitively (Figure 2). It is still widely debated whether APOE also influences Aβ synthesis, given that it controls lipid metabolism and that problems with lipid regulation are associated with elevated brain Aβ production. Aβ has the ability to influence the internalization of APOE, which in turn modulates it. When Aβ is present, APOE3 and APOE4 bind to LDL receptors, undergo conformational changes, and undergo significant internalization. This leads to an overall rise in Aβ uptake by APOE4-mediated neurons, with APOE4 exhibiting a more robust rise in binding to hippocampal neurons than APOE3. The intracellular amyloid precursor protein (APP) recycling process can be impacted by the internalization and increased domain interaction of APOE4 with LDL receptors, leading to an additional increase in Aβ load through enhanced Aβ production [19].

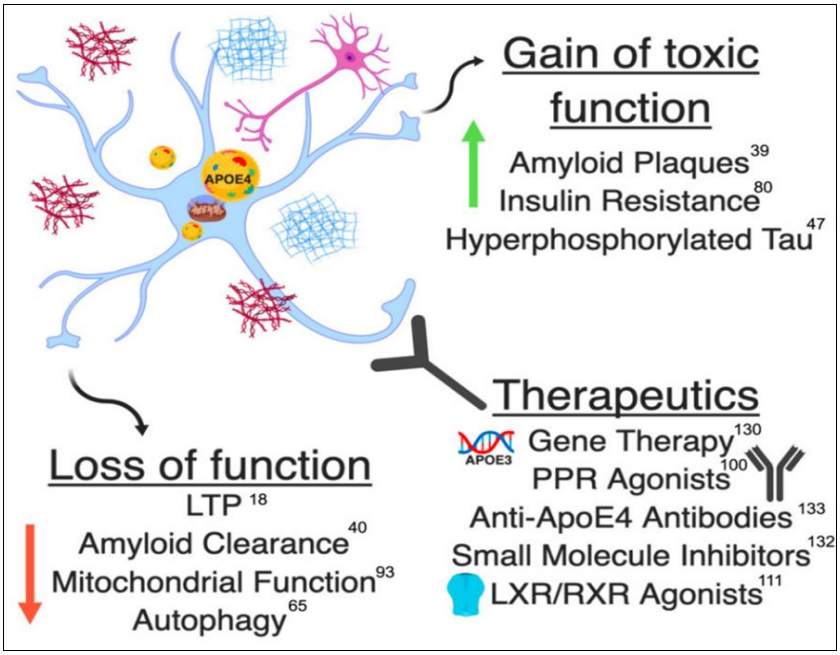

Fig 2: ApoE4's impact on AD pathology [20]

Although the focus of Alzheimer's disease research has moved away from the amyloid cascade hypothesis and towards τ, inflammation, metabolism, and hyperactivity, the potential role of APOE4 in Aβ pathology should still be considered as a target for treatments that modify the disease. By determining the time interval between the presence of Aβ deposits and disease, therapeutic intervention becomes more feasible, as Aβ deposits can be detected in the brain years prior to the onset of clinical symptoms. Instead of focusing on eliminating the plaque load entirely or targeting amyloid with antibodies, future treatments may aim to reduce APOE/Aβ competition or improve Aβ clearance through increasing LRP1 expression or dysfunction [21].

The relation between psoriasis and cognitive impairment

Medical and social support are necessary for people with psoriasis because it is a chronic condition. Multiple disabilities, including physical and mental impairments, can develop in patients with long-term psoriasis. Social stigma and psychological problems are common outcomes of psoriasis, a chronic, disabling disorder. Relapses of psoriasis, brought on by emotional or mental distress, can worsen an already dismal prognosis. When it comes to one's physical and mental health, nothing is more important than primary care and early psychological intervention.

.A study done by Luiza Marek-Józefowicz [22] The dorsolateral prefrontal cortex functions were assessed in a total of 188 participants (91 healthy controls and 97 psoriasis patients) using the Stroop and Trail Making tests. Psoriasis severity was assessed using the PASI index. Neuropsychological assessments of memory and executive function showed that psoriatics performed worse than healthy individuals.

Psoriasis patients show early deficits in attention, executive functions, and long-term verbal memory, making them more likely to develop dementia compared to patients with a single domain mild cognitive impairment (MCI). Involvement of the subcortical frontal regions of the brain is suggested by the pattern of errors in cognitive tests of psoriasis patients. The majority of patients also performed poorly on free recall and Weigl's tests, suggesting that they are unable to use semantics and other cognitive strategies for long-term memory retention [23].

Patients with other systemic diseases, such as psychiatric, inflammatory, or metabolic disorders, are more likely to experience cognitive impairment at an earlier age, according to a study. Dementia was determined to be a leading cause of mortality for people with severe psoriasis in the UK, as compared to the general population. Psoriasis and Alzheimer's disease may share a shared genetic background. Both disorders have been linked to polymorphisms in the apolipoprotein E gene, specifically the Apo e4 allele. Patients with psoriasis exhibited signs of cognitive dysfunction linked to activity in the prefrontal cortex. They also had problems with free recall and Weigl's tests, suggesting that they couldn't use different strategies, such as semantics, to remember things [24].

In two areas of working memory, neuropsychological testing showed that people with psoriasis performed worse than healthy controls. Longer execution times in both parts

of the TMT test—which measures visual-spatial working memory—suggest that psoriasis patients have slower psychomotor speed, less efficiency, and poor visual memory. Patients with psoriasis also outperformed healthy controls on a test of verbal memory [25].

Researchers have linked chronic plaque psoriasis to mild cognitive impairment (MCI) and have proposed a role for psoriasis in the development of cognitive impairment. A comprehensive neurological evaluation may be necessary to identify early mild cognitive impairment in patients with psoriasis, and systemic treatment for psoriasis may alleviate cognitive impairment. Researchers observed that individuals' psychomotor speed and verbal memory ability declined as the intensity of depression dimension scale TEMPS-a increased. Reduced spatial memory and psychomotor efficiency were associated with higher levels of anxiety on the TEMPS-A dimension [26].

Alzheimer's disease

Nearly half to three quarters of all occurrences of dementia are caused by Alzheimer's disease, making it the most common form of dementia. Being the leading cause of dementia, it will ultimately take away people's capacity to live on their own. Despite decades of research, the pathogenic mechanism of Alzheimer's disease is still unknown, and no medication has been found to halt the disease's progression or even provide a cure. The most common theory about the origins of Alzheimer's disease proposes that beta-amyloid peptide (Ab) buildup and hyperphosphorylated tau are involved. However, there is a flaw in this theory; rather than treating AD based on reversible stages, it was permitted to be treated as a curable disease [27].

According to the 2018 Alzheimer's Disease International World Alzheimer Report, "state of the art of dementia research: new frontiers," published in 2018, women are more likely than men to develop Alzheimer's disease, especially after the age of 80. Even though the amyloid β burden is similar, women may be affected by a higher tau load. When looking at the likelihood of developing Alzheimer's disease, twin studies have shown that heredity accounts for 60-80% of the variation. The common APOE ε4 allele can explain a significant portion of Alzheimer's disease, although it does not fully explain its heredity. Massive genome-wide association studies have raised the number of risk alleles for Alzheimer's disease to over 40, allowing researchers to better target their hunt for new genetic variants. Carriers of the protective APOE ε2 allele had a lifetime risk of Alzheimer's disease that was almost two times lower than noncarriers. Put simply, the chances of developing Alzheimer's disease are extremely low for people who carry the homozygous APOE ε2 genotype [28].

Fundamental researchers referred to the early stages of Alzheimer's disease as the cellular phase. Changes in microglia, neurons, and astroglia pushed the disease steadily along before cognitive impairment was noticed. Alterations in the vascular system, dysfunction of the lymphatic system, neuroinflammation, and aging all operate either before or alongside the accumulation of amyloid β in this cellular illness milieu. The cellular pathology of Alzheimer's disease is the main focus of research, but a lot is still unknown about the biochemical stage that comes before it. Research on the function of pure γ-secretase complexes revealed that they are prone to aggregation. Furthermore, the early release of longer amyloid β peptides is caused by clinical mutations in presenilins that interfere with the connections between γ-secretase and APP. The results of this study lend support to the idea that amyloid beta could be a target for Alzheimer's disease treatments [29].

There is no doubt that the peripheral immune system, the gastrointestinal microbiota, the brain's clearance systems (including the glymphatic, vasculature, and other systems), and the blood-brain barrier all have a role in how the disease manifests clinically. Pathologies in the circulatory system can also compromise the blood-brain barrier. There has been great strides in understanding the genetic underpinnings and pathophysiology of Alzheimer's disease. Maintaining this rate will allow for the eventual implementation of multimodal treatment plans and the identification of patients at very early stages [30].

The relation between psoriasis and Alzheimer

Researchers have looked into the possible connection between psoriasis and Alzheimer's disease, two inflammatory illnesses. Risk ratios ranging from 1.10 to 1.25 indicate that those with psoriasis are more likely to develop Alzheimer's disease. Patients with dementia who simultaneously acquire psoriasis are at an increased risk. On the other hand, psoriasis was found to be protective against Alzheimer's disease in a 2008 study. In addition, a new meta-analysis indicated that vascular and non-vascular dementia were more common in psoriasis patients than in those without the disease. A population-based case-control cohort study in Korea investigated the potential link between psoriasis and Alzheimer's disease and found that patients with psoriasis had a slightly increased risk of developing the condition compared to those without it. Psoriasis patients had an increased risk of mild cognitive impairment, which affects verbal memory, executive function, and visuospatial ability, among other things, according to the study's authors [31].

Pathogenesis

It is still not known what causes psoriasis and Alzheimer's disease. In psoriasis, keratinocytes are affected by cytokines including IL-23 and TNFα, which are produced by dendritic cells and activated T cells. *in vivo*, TNF-α can worsen tau and Aβ pathologies and hence play a crucial role in the development of Alzheimer's disease. Agents that inhibit tumor necrosis factor-alpha can enhance cognitive performance in Alzheimer's disease patients. Research has shown that psoriasis patients who take TNF blocking medications such adalimumab, infliximab, or etanercept are less likely to acquire Alzheimer's disease compared to people who do not take these medications [32].

When treating psoriasis, monoclonal antibodies often target the IL-12/IL-23 common subunit p40, which is one of the most significant axis in the disease's progression. According to recent reviews, the IL-23/IL-12A axis is crucial in the pathophysiology of inflammation linked with aging, as seen in Alzheimer's disease. Simultaneously, they discovered that the p40 level in cerebral fluid was elevated in the Alzheimer's disease mice model. Furthermore, they found that blocking p40 alleviated cognitive deficits and reduced the number of Aβ plaques [33].

Genetic studies provide more evidence linking psoriasis and Alzheimer's disease. At the genetic level, apolipoprotein E (APOE) is the strongest marker for Alzheimer's disease. It is the principal carrier of cholesterol and has a notable influence on Aβ deposition and tau phosphorylation, in

addition to being linked to cardiovascular diseases and other neurological disorders. Similarly, multiple studies have demonstrated that APOE genotypes independently increase the likelihood of developing and exacerbating psoriasis. There were eight polymorphisms and two pleiotropic loci associated with the other six diseases, including psoriasis and Alzheimer's. That inflammation plays a role in the onset of Alzheimer's disease is borne out by this discovery [34].

Due to these commonalities, the advantages of addressing psoriasis as a systemic illness have been highlighted. Dementia was less common in psoriasis patients who took systemic anti-inflammatory medication for three months or longer, according to a cohort study. Patients with psoriasis were likewise split into two groups in a Korean study: one that used systemic therapy and another that did not. Systemic therapy dramatically reduced the probability of getting Alzheimer's disease compared to both the no-systemic-therapy group and individuals without psoriasis [35].

Conclusion

Serum beta-amyloid levels are associated with psoriasis vulgaris and play a predictive role in its occurrence. Additionally, the presence of cognitive impairment and depression in psoriasis patients may highlight the broader systemic impact of the disease, suggesting a potential link between psoriasis and cognitive decline.

Conflict of Interest

Not available

Financial Support

Not available

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How to Cite This Article
Abdulmohsin GN, Kadhum BQ, Abdel-Khalek GM, El-Ghafar AOA, Sabry HH, Mahmoud MM. The link between serum beta-amyloid and serum apolipoprotein E4 in psoriasis and cognitive impairment. International Journal of Dermatology, Venereology and Leprosy Sciences. 2025;8(1):06-12.