Dermatology Practical & Conceptual

Cognitive Decline and Neurodegenerative Markers in Psoriasis: The Role of APOE4 and Beta-Amyloid

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ABSTRACT

Introduction: Psoriasis vulgaris (PV) is a chronic inflammatory skin disease increasingly recognized as a systemic disorder with potential cognitive implications. Amyloid beta (Aβ) and apolipoprotein E (APOE) are key proteins involved in Alzheimer's disease (AD) and neurodegeneration.

Objectives: This study investigated the relationship between PV, cognitive function, and serum levels of Aβ and APOE4.

Methods: This case-control study was conducted on 80 participants: 50 PV patients and 30 age- and sex-matched controls. Clinical assessments included Psoriasis Area and Severity Index (PASI). Depression severity was assessed with Beck Depression Inventory-II (BDI-II), while cognitive function was evaluated using Montreal Cognitive Assessment (MoCA). Serum APOE4 and Aβ levels were measured using ELISA.

Results: Patients with PV exhibited significantly higher levels of APOE4 (1125.5 ± 232.1 ng/ml vs. 821.8 ± 266 ng/ml, $P<0.001$) and Aβ (21.4 ± 2.2 ng/ml vs. 18.7 ± 1.4 ng/ml, $P<0.001$) compared to controls. ROC analysis identified APOE4 (AUC=0.80, $P<0.001$) and Aβ (AUC=0.86, $P<0.001$) as significant predictors of PV. MoCA scores were significantly lower in PV patients (median=22 vs. 28, $P<0.001$), particularly in those with severe disease. APOE4 and Aβ levels negatively correlated with cognitive function (r= -0.418, $P=0.003$), and (r= -0.399, $P=0.004$) respectively.

Conclusions: PV is associated with elevated Aβ and APOE4 levels, potentially linking chronic inflammation to neurodegeneration. The observed cognitive dysfunction in PV individuals underscores the importance of integrating neurological assessments into routine clinical evaluations.

Introduction

Psoriasis vulgaris (PV) is a prevalent chronic inflammatory disorder with a multifactorial etiology, affecting approximately 1–2% of the population. It manifests with diverse clinical presentations, predominantly involving skin and joints [1]. Symptom severity, including pruritus and pain, varies widely among individuals. However, its impact on quality of life is consistently substantial, frequently contributing to psychological comorbidities such as anxiety and depression [2].

Psoriasis was historically viewed as a dermatologic condition marked by episodic flare-ups and remissions [3]. However, the perception of psoriasis as a solely skin-related disorder is now considered obsolete. Emerging research underscores its classification as a systemic immune-mediated disease with a broad spectrum of comorbidities [4].

Among these comorbidities, accumulating evidence indicates an increased susceptibility to Alzheimer's disease (AD) in individuals with psoriasis, with reported risk ratios ranging from 1.10 to 1.25. Conversely, patients with dementia also exhibit a higher prevalence of psoriasis, suggesting a potential bidirectional relationship between the two conditions [4,5].

AD is a progressive neurodegenerative disorder and a leading cause of dementia in older adults, with an estimated global prevalence of 30 million cases in 2015 [6]. While its exact pathogenesis remains incompletely understood, it is thought to result from a complex interaction of genetic susceptibility and environmental factors that contribute to neuroinflammation. Growing evidence implicates dysregulated immune mechanisms, particularly T helper (Th)1/Th17 cells and proinflammatory cytokines, both of which are also central to psoriasis, in AD neurodegenerative processes. The defining pathological features of AD include accumulation of neurofibrillary tangles and amyloid plaques in brain [7-9].

Apolipoprotein E (APOE) and amyloid-beta (Aβ) have been extensively studied in relation to AD and various forms of cognitive dysfunction [10]. Research indicates that accumulation of Aβ plaques and tau protein abnormalities significantly heighten cognitive decline risk and dementia [11,12]. Among APOE isoforms, ε4 allele is a well-recognized genetic risk factor that modulates Aβ deposition and clearance in brain, thereby influencing trajectory of neurodegenerative diseases. Notably, cognitive impairment is frequently accompanied by depression, with systemic inflammation emerging as a shared pathogenic mechanism linking the two conditions [13].

The association between psoriasis and cognitive impairment is likely driven by a combination of genetic susceptibility, chronic systemic inflammation, and immune dysregulation. Inflammation is a key factor in psoriasis, with elevated levels of proinflammatory markers such as TNF-alpha and IL-6 observed in both psoriasis and neurocognitive disorders [14]. Persistent systemic inflammation may contribute to neuroinflammation, facilitating accumulation of Aβ and tau proteins in brain, which are hallmarks of neurodegeneration. Additionally, high prevalence of stress and depression among individuals with psoriasis may further amplify inflammatory pathways, reinforcing connection between these conditions through overlapping pathogenic mechanisms [15].

Objectives

This study investigated serum levels of Aβ and APOE in patients with psoriasis and assessed their cognitive function to identify potential links between psoriasis and cognitive impairment.

Methods

Study Design

This prospective case-control study was carried out on 80 participants (50 patients with a clinical diagnosis of chronic plaque-type PV; the **control group** included 30 age- and sex-matched healthy individuals without PV) at Dermatology Outpatient Clinic at Benha University Hospitals.

Eligibility Criteria

The study included patients diagnosed with chronic plaque-type PV aged between 18 and 60 years. Patients were excluded if they had received systemic anti-psoriatic treatments or phototherapy within the past month or had used topical treatments within the past two weeks. Additional exclusion criteria were presence of autoimmune, inflammatory, or cutaneous disorders, metabolic, endocrine, or neurological conditions that could affect cognitive function (such as diabetes or hypertension), pregnancy or suspected pregnancy, mental retardation. major psychiatric disorders (e.g., schizophrenia, bipolar disorder, or history of psychosis), alcohol use or addiction, and significant communication difficulties (e.g., blindness or deafness).

All Participants Underwent a Comprehensive Assessment

A detailed medical history was taken covering personal data, history of other skin or systemic diseases, family history of psoriasis, and previous treatments. A clinical examination was conducted. Additionally, a thorough dermatological evaluation was performed to assess current symptoms and disease onset and course as well as type, location, distribution, and severity of psoriasis using PASI [16].

Serum levels of APOE4 and Aβ were quantified from blood samples collected from antecubital veins of both patients and control participants using Vacutainer® blood collection tubes between 8:00 AM and 10:00 AM. All participants fasted for 12 hours prior to venipuncture. Serum was separated within 30 minutes of collection and subsequently stored at –70° C until analysis. Quantification was performed using ELISA kits, adhering strictly to the manufacturer's protocols.

Serum APOE4 levels were assessed using Human APOE4 ELISA Kit (Catalog No: DL-APOE4-Hu; DLDEVELOP, Wuxi, China), while serum Aβ levels were determined with Human Beta-Amyloid Peptide (Ab) ELISA Kit (Catalog No: DL-Ab-Hu; DLDEVELOP, Wuxi, China).

The psychometric assessments employed in this study were chosen for their robust reliability and validity. Depression severity and diagnosis were evaluated using the validated Arabic version of Beck Depression Inventory-II (BDI-II) [17]. Global cognitive function was assessed with MoCA [18], utilizing the Arabic version validated by Rahman and Gaafary [19].

Sample Size Calculation

The sample size was determined using Epi Info software (version 7.2.5.0) based on an estimated psoriasis prevalence of 3% in adults [20]. Assuming a 95% confidence level and a 5% margin of error, the required sample size was calculated to include 50 patients with psoriasis.

Statistical Methods

Statistical analyses were conducted using SPSS software (version 28, IBM, Armonk, NY, USA). The normality of quantitative data was evaluated using the Shapiro-Wilk test and direct visualization techniques. Continuous variables were summarized as means with standard deviations or as medians with ranges, while categorical data are presented as frequencies and percentages based on the distribution. Comparisons of continuous variables across groups were performed using the independent t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Categorical variables were analyzed using the chi-square test. Receiver operating characteristic (ROC) curve analysis was conducted to assess the diagnostic efficacy of APOE4 for PV, including the calculation of the area under the curve AUC, 95% confidence intervals, appropriate cutoff points, and diagnostic indices. Correlations were evaluated with Pearson's or Spearman's correlation coefficients, if applicable. APOE4 and Aβ levels were evaluated across several patient subgroups using independent t-tests, whilst BDI-II and MoCA scores were assessed by the Mann-Whitney U test. Multivariate logistic regression analysis was conducted to identify determinants of PV, with odds ratios (ORs) and 95% confidence intervals (CIs). Furthermore, multivariate linear regression analyses were performed to forecast BDI-II and MoCA scores, with regression coefficients and their respective 95% confidence intervals computed. All statistical tests were two-sided, and p-values less than 0.05 were deemed statistically significant.

Results

General Characteristics and Clinical Findings

Both study groups were comparable in terms of age (P=0.537), sex (P=0.954), smoking habits (P=0.356), education level (P=0.199), and body mass index (BMI; P=0.18). All patients exhibited plaque psoriasis. Additionally, 56% reported nail psoriasis, and 32% experienced psoriatic arthritis. The most common severity of psoriasis was moderate (40%), followed by mild (34%) and severe (26%). The median PASI score was 6.6, with a range of 1.6 to 44.5. All patients had a gradual disease onset. Over half (58%) experienced periods of remission and exacerbation, while approximately one third (42%) had a progressive disease course. The median disease duration was 4.5 years, ranging from 0.5 to 18 years.

APOE4 & Aβ Levels

Patients with PV demonstrated significantly higher levels of both APOE4 and Aβ compared to controls (1125.5 ± 232.1ng/ml vs. 821.8 ± 266 ng/ml, P<0.001; 21.4 ± 2.2 ng/ml vs. 18.7 ± 1.4 ng/ml, P<0.001, respectively) (Figure 1).

ROC Analysis of APOE4 & Aβ

ROC analysis was conducted for APOE4 and Aβ to diagnose PV. APOE4 showed a significant AUC of 0.8, with 95% CI: 0.703–0.897 (P<0.001). The optimal cutoff value was >991, yielding a sensitivity of 72%, specificity of 80%, positive predictive value (PPV) of 85.7%, and a negative predictive value (NPV) of 63.2%. For Aβ, ROC analysis indicated an AUC of 0.858 with 95% CI: 0.780–0.937 (P<0.001). The optimal cutoff was >19.9, with a sensitivity of 72%, a specificity of 86.7%, PPV of 90%, and NPV of 65% (Figure 2).

APOE4 & Aβ as Predictors of PV

A multivariate logistic regression analysis identified APOE4 serum level as a significant predictor of PV, with an OR of

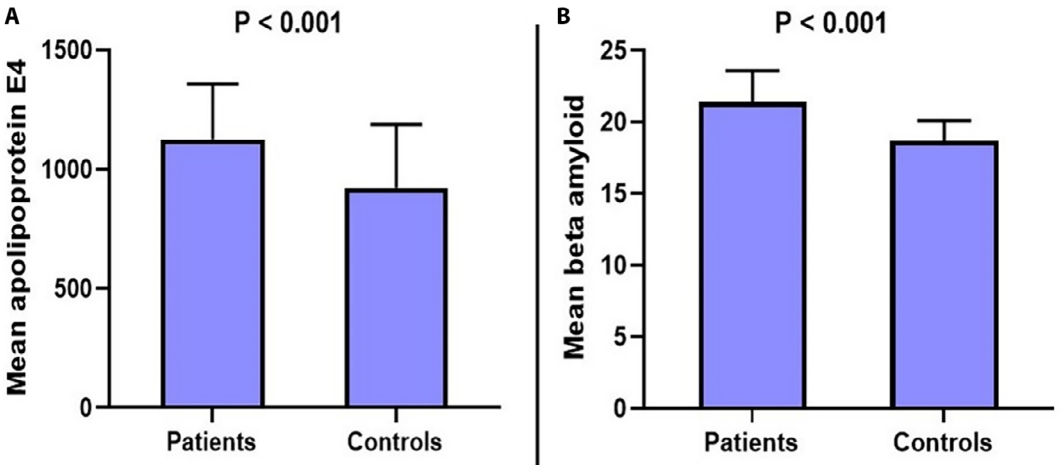

Figure 1. A) APOE4 and B) beta-amyloid serum levels (ng/ml) in the studied groups.

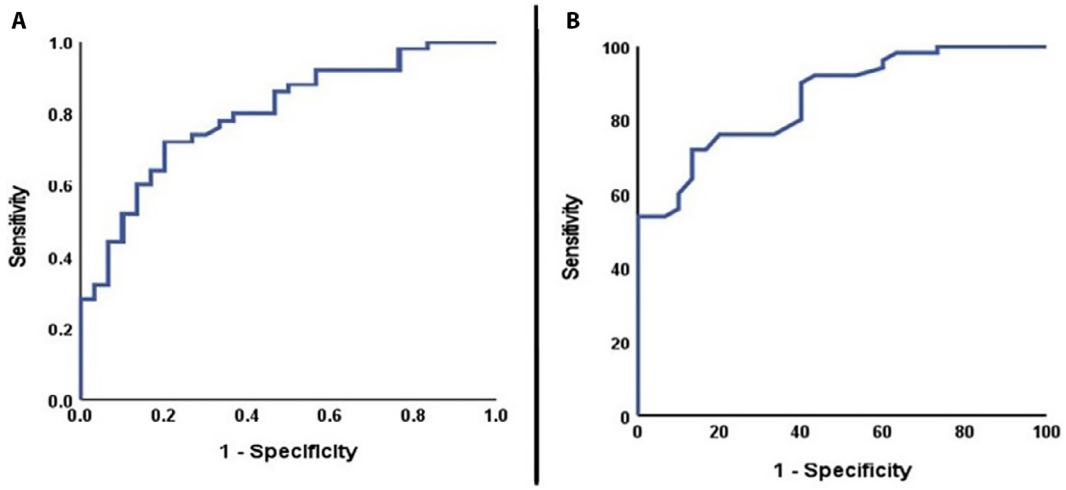

Figure 2. ROC analysis of A) APOE4 and B) Beta-amyloid to diagnose PV.

1.005 (95% CI: 1.003–1.008; *P*<0.001), after adjusting for age, sex, smoking status, and BMI. Similarly, Aβ was also found to be a significant predictor of PV; a one-unit increase in Aβ was associated with an approximately threefold increase in the risk of developing psoriasis (OR=2.64, 95% CI: 1.666–4.186; *P*<0.001), while controlling for the same confounding variables.

Depression and Cognitive Functions Assessment

The median BDI-II score was notably higher in cases compared to controls (15 vs. 0, respectively, *P*<0.001). Furthermore, there were notable variations in depression severity between the two groups (*P*=0.005). The patients exhibited a higher prevalence of depression, showing mild (30%), moderate (26%), and severe (2%) depression degrees, while 42% had a BDI-II score in the normal range. In contrast, controls demonstrated a higher proportion of those with minimal or no depressive symptoms (80%), followed by those with mild (13.3%) and moderate (6.7%) depression degrees.

PV patients demonstrated significantly lower total MoCA score when compared to PV-free control subjects (median=22 vs. 28, *P*<0.001).The patients demonstrated considerably lower scores than controls in the following domains: executive (*P*=0.003), attention (*P*=0.005), and recall (*P*=0.002), while naming (*P*=1.0), language (*P*=0.096), abstraction (*P*=0.187), and orientation domains (*P*=1.0) were not notably different between both groups (Figure 3).

Total MoCA score differed significantly according to severity of PV (*P*=0.009). Total MoCA score had significantly lower values in severe versus mild PV (*P*=0.009) and in severe versus moderate PV (*P*=0.035) (Table 1).

Multivariate linear regression analysis was performed to predict BDI-II and MoCA scores while controlling for age, sex, smoking, educational level, and BMI. Aβ and APOE4 serum levels were not significant predictors of BDI-II scores; however, both were significant predictors of MoCA scores in PV patients. Aβ serum levels negatively predicted MoCA scores (B= -1.228, 95% CI: -1.877– -0.579, *P*<0.001), while

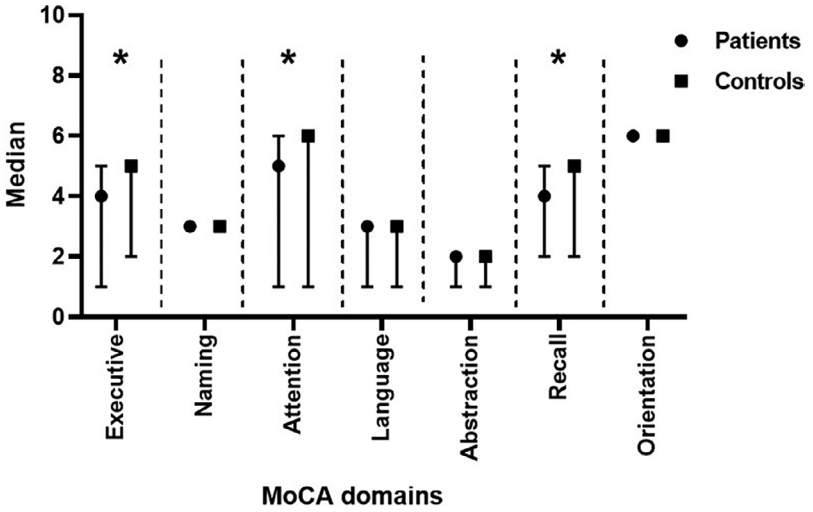

Figure 3. Montreal Cognitive Assessment (MoCA) domains in PV patients versus control subjects

Table 1. MoCA score in different degrees of severity of PV.

Severity of psoriasis	No (%)	MoCA score (Mean ± SD)	P-value
Mild	17 (34)	26.41 ± 4.08 [3]	0.009*
Moderate	20 (40)	26.45 ± 3.33 [3]	
Severe	13 (26)	21.62 ± 5.36 [1,2]	

MoCA: Montreal Cognitive Assessment; PV: psoriasis vulgaris; SD: standard deviation; *: significant p-value <0.05, [1]: significantly different from mild group; [2]: significantly different from moderate group; [3]: significantly different from severe group

APOE4 serum levels positively predicted MoCA scores (B= –0.005, 95% CI: –0.007– –0.002, *P*=0.002).

Correlation between APOE4, Aβ and other Parameters

APOE4 levels demonstrated a significant positive correlation with Aβ levels (r= 0.374, *P*=0.007) and a strong positive correlation with PASI score (r=0.488, *P*<0.001). Additionally, MoCA scores exhibited a significant negative correlation with APOE4 levels (r= -0.418, *P*=0.003). Other variables, including age (*P*=0.515), BMI (*P*=0.889), duration of illness (*P*=0.692), and BDI-II scores (*P*=0.127), were not significantly associated with APOE4 levels.

Aβ levels showed a significant negative correlation with total MoCA scores (r= -0.399, *P*=0.004), while demonstrating significant positive correlations with age (r=0.506, *P*<0.001), BMI (r=0.350, *P*=0.013), PASI score (r=0.402, *P*=0.004), disease duration (r=0.396, *P*=0.004), and BDI-II scores (r=0.345, *P*=0.014).

APOE4 & Aβ according to Other Parameters

Higher levels of APOE4 were observed in individuals with nail psoriasis compared to those without (*P*=0.011), while there was no significant difference based on sex, smoking status, presence of psoriatic arthritis, or disease course. Conversely, Aβ levels were lower in males and non-smokers and were significantly higher in patients with a progressive disease course (*P*<0.05 for all) and those with nail psoriasis. No significant difference in Aβ levels was noted with presence of psoriatic arthritis (Table 2).

Discussion

PV is a chronic immune-mediated disease affecting the skin and joints, often accompanied by systemic inflammation and comorbidities, including cognitive impairment [21]. While traditionally considered a dermatological condition, growing evidence suggests a link between PV and neurodegenerative disorders such as AD [15]. AD, characterized by amyloid plaques and neurofibrillary tangles, shares inflammatory pathways with PV, particularly involving Th1/Th17 cells and cytokines. Aβ and APOE play critical roles in AD pathogenesis, influencing cognitive decline through amyloid accumulation and neuroinflammation [22]. Given the shared inflammatory mechanisms between PV and cognitive disorders, this study aimed to investigate serum levels of Aβ and APOE in psoriasis patients and assess their cognitive function to explore potential associations.

The elevated levels of APOE4 and Aβ in PV patients align with previous findings suggesting that chronic inflammation

Table 2. APOE4 & beta-amyloid according to other parameters in the studied patients.

	APOE4	p-value	Beta-amyloid	p-value
Sex				
Males	1107.1 ±211.4	0.532	20.8 ±1.8	0.017 *
Females	1149 ±259.4		22.2 ±2.4	
Smoking				
Yes	1175.7 ±246.7	0.098	22.2 ±2.3	0.003*
No	1066.6 ±203.4		20.5 ±1.6	
Nail psoriasis				
Yes	1198.2 ±190.4	0.011*	22.1 ±2.1	0.013*
No	1033.1 ±251.3		20.6 ±2	
Psoriatic arthritis				
Yes	1143.4 ±197.5	0.713	20.7 ±2.3	0.122
No	1117.1 ±249.1		21.7 ±2.1	
Course				
Progressive	1135.2 ±237.6	0.806	22.8 ±2.1	<0.001*
Remission & exacerbations	1118.6 ±232.1		20.4 ±1.6	

APOE4: Apolipoprotein E4; BMI: body mass index; BDI-II: Beck Depression Inventory-II; MoCA: Montreal Cognitive Assessment; PASI: Psoriasis Area and Severity Index; PV: psoriasis vulgaris; *: significant p-value <0.05.

may contribute to neurodegenerative processes. APOE4, a key genetic risk factor for AD, is involved in lipid metabolism dysregulation and impaired Aβ clearance in brain [23]. Systemic inflammation in psoriasis may exacerbate Aβ accumulation, a hallmark of AD pathology [7]. The observed positive correlation between APOE4 and Aβ levels further supports a potential interplay between these biomarkers in psoriasis.

The ROC analysis demonstrated that both APOE4 and Aβ could serve as diagnostic markers for psoriasis, with significant AUC values. This finding aligns with growing evidence that systemic inflammation in psoriasis may contribute to neurodegenerative diseases [24]. The elevated levels of these biomarkers in PV patients suggest a shared pathogenic pathway involving chronic inflammation and immune dysregulation, common to both psoriasis and cognitive disorders [25].

PV patients exhibited significantly lower MoCA scores than controls, particularly in executive function, attention, and recall. This finding aligns with previous studies reporting cognitive deficits in individuals with chronic inflammatory diseases, including psoriasis [14].

The negative correlation between Aβ levels and MoCA scores further supports the hypothesis that systemic inflammation in psoriasis may contribute to cognitive decline through mechanisms such as neuroinflammation and amyloid-beta accumulation [26].

The Th17 role in neurodegenerative diseases, particularly AD, has been highlighted in the literature [27]. Aβ may contribute to the activation of Th17/IL-17 axis and initiation of an inflammatory cascade, either directly through oxidative stress or indirectly by disrupting blood-brain barrier [28].

The severity of psoriasis, as indicated by PASI score, was also correlated with reduced cognitive performance, with the most pronounced impairment observed in patients with severe disease. This finding is consistent with previous research suggesting that the systemic inflammatory burden in psoriasis may exert a dose-dependent impact on cognitive function [14]. The higher prevalence of depression in PV patients, as indicated by elevated BDI-II scores, may further exacerbate cognitive impairment, as depression is known to negatively impact cognitive function [29].

The elevated APOE4 levels in psoriasis patients may result from multiple interconnected mechanisms. Chronic systemic inflammation, a hallmark of psoriasis, may upregulate APOE4 as part of body's inflammatory response [30]. Additionally, psoriasis is frequently associated with dyslipidemia, and given APOE4's central role in lipid metabolism, altered lipid profiles in psoriatic patients may further contribute to increased APOE4 levels. Genetic predisposition also plays a role as certain APOE gene variants linked to lipid metabolism may increase susceptibility to both psoriasis and elevated APOE4 levels. Furthermore, neuroinflammatory pathways associated with psoriasis, which can impact cognitive function, could enhance APOE4 expression, potentially linking disease to cognitive decline [31].

The higher prevalence of depression in PV patients aligns with previous research highlighting significant psychological burden of psoriasis [2]. Depression in psoriasis likely results from both psychosocial impact of disease and systemic

inflammatory processes contributing to mood disorders [15]. The absence of a significant correlation between depression scores and APOE4 or Aβ levels suggests that depression in psoriasis may be primarily driven by psychosocial factors rather than neurodegenerative processes.

The significantly higher APOE4 and Aβ levels in patients with nail psoriasis may reflect a greater inflammatory burden in these individuals. Additionally, elevated Aβ levels in patients with a progressive disease course suggest that chronic inflammation may drive amyloid-beta accumulation over time. These findings support the hypothesis that systemic inflammation in psoriasis could contribute to neurodegenerative changes [5].

This study has several limitations that should be acknowledged. While the sample size was sufficient for statistical analysis, it may not fully capture the heterogeneity of psoriasis and its associated comorbidities. Moreover, potential confounding factors, including dietary habits, physical activity, and other lifestyle influences on cognitive function and inflammatory markers, were not accounted for in this study.

Conclusions

PV is associated with elevated Aβ and APOE4 levels, suggesting a potential link between chronic inflammation and neurodegeneration. The observed cognitive impairment in PV patients highlights the importance of neurological assessments in clinical practice.

Ethical Approval: The research protocol received approval from the Ethics Committee at Benha University. Informed consent was gathered from all participants. The authors affirm that all actions conducted in studies with human participants adhered to the ethical guidelines of the relevant institutional and/or national research committees, as well as to the principles outlined in the 1964 Helsinki Declaration and its subsequent revisions or equivalent ethical standards.

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