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Correlation of Retinal Sensitivity in Psoriasis and Psoriatic Arthritis with Tumour Necrosis Factor Alpha and Pigmented Epithelium Derived Factor

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ABSTRACT

Background: Early recognition is crucial because the natural course of psoriasis (Ps) may result in vision loss. Psoriatic arthritis (PsA) patients with ophthalmological manifestations of psoriasis (Ps) account for 30% of cases. Assessment of visual functions and correlation with blood levels of tumour necrosis factor-alpha (TNF- α) and pigmented epithelium derived factor (PEDF) were the study's main goals in Ps and PsA patients.

Objectives: to assess visual functions in Ps and PsA patients and correlate them with serum levels of tumour necrosis factor-alpha (TNF-α) and Pigmented Epithelium Derived Factor (PEDF).

Subjects &Methods: This case-control study involved 60 Ps patients, 30 of whom had Ps without arthritis and 30 of whom had PsA, 30 age and sex-matched healthy individuals were included, representing the control group. Serum levels of both TNF-α and PEDF were measured by enzyme-linked immune sorbent assay and complete ophthalmological examination of the anterior and posterior segment by slit-lamp Biomicroscopy, best corrected visual acuity, intraocular pressure, and visual field using automated perimetry.

Results: Visual affection in PsA patients was affected more than psoriatic patients with positive correlation with serum TNF-α level and negative correlation with PDF. High statistically significant increase in serum TNF-α level with the severity of both Ps and PsA P= 0.000. Also, high statistically significant increase in mean deviation (MD) and increase the negativity of PSD. High statistically significant increase in TNF and decrease in PEDF levels were found between patients and control (p = 0.001) with a higher significant difference (p =0.000) in PsA patients

Conclusion: To prevent vision impairment, patients with Ps and PsA should receive routine ophthalmological tests to evaluate their visual functions and spot potential ocular involvement.

Keywords: Visual affection, Ps Vulgaris, Psoriatic Arthritis, TNF-α, PEDF.

INTRODUCTION

In particular, ocular manifestations of psoriasis, which is an immune-mediated, chronic inflammatory disease with genetic underpinnings, have been noted. These manifestations include reduced retinal sensitivity, retinal disorders, blepharitis, dry eye, conjunctivitis, keratitis, uveitis, and birdshot chorioretinopathy [(1)]. The severity of Ps vulgaris has an impact on the retinal sensitivity [(2)].

TNF-α is essential for a healthy immune response. The immune system can be activated to regulate by TNF-α, but excessive or improper TNF-α production can be damaging and can result in Ps and PsA [(3)]. Bone remodeling encourages osteoclastogenesis by increasing the frequency of osteoclast precursor cells and upregulating receptor activator of nuclear factor kappa-B ligand (RANKL) in synovial tissue, which causes increased bone resorption. TNF-α is a dominant cytokine in PsA [(4)].

One of the most prevalent adipokines, PEDF is found in a variety of human tissues [(5)].

It is a secreted protein with multiple activities, including anti-angiogenic, anti-metastatic, anti-inflammatory, antioxidative, and neurotrophic. It has primarily been investigated in the eye, where disorders like age-related macular degeneration and diabetic retinopathy cause changes in its levels there [(6)].

PATIENTS AND METHODS

This case-control study included 60 patients (30 patients with Ps Vulgaris) and the patient group (which included 30 people with psoriatic arthropathy) was chosen. A control group of 30 healthy people who were matched for age and sex was also included. The study was conducted between January 2020 and January 2022, all patients were drawn from Al-Zahraa University Hospital's Outpatient Clinic.

Inclusion criteria: This study included patients with Ps Vulgaris and PsA who were diagnosed using the CASPAR criteria for PsA and were aged from 20 to 50 years.

Exclusion criteria: Other autoimmune diseases such systemic lupus erythematosus, rheumatic, high uric acid, vasculitis, neurological diseases, and space-occupying lesions). Systemic or ocular disease, hypertension, diabetes mellitus, and other autoimmune diseases. Color vision issues, cataracts, uveitis, the use of systemic topical retinoic acid or immunosuppressive medications, and UV therapy. Optic neuropathy, high refractive errors, glaucoma, retinal detachment, retinal pigment changes, and active or past retinol choroiditis.

Ocular examination: Best corrected visual acuity (BCVA) at a distance using Landolt's C chart and assessment of the refractive status using an auto

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refractometer (KR-8100; Topcon Corporation, Tokyo, Japan).

Complete ophthalmological examination of the anterior segment by Slit-lamp bio-microscopy.
Measurement of intraocular pressure: Done by Goldman applanation tonometry.
Fundus examination: To assess retina and optic disc by 90 D Volk non-contact lens.

Visual field using automated perimetry:

Patients are evaluated using Standard Automated Perimetry (SAP) and the Humphrey, Carl Ziess Meditec, Inc., model (745i), middle 30-2 Interactive Threshold Swedish Algorithm (SITA standard). These features (fixation loss of less than 20%, false positive rate of less than 33%, false negative rate of less than 33%) were dependable even though only one eye from each subject was employed in the study. Global indices' mean deviation (MD) and pattern standard deviation (PSD) were evaluated.

All patients were subjected to full history taking, routine laboratory investigations, ESR, RF, and C-reactive protein (CRP). Ps Area & Severity Index (PASI) score (0-72) was used to assess the severity and extent of skin disease. Plain radiographs were done as routine evaluation by doing anteroposterior and lateral views for the joints of hands, feet, and sacroiliac joints.

All patients were examined Rheumatologically for any joint or axial involvement. Thirteen patients were fulfilling the classification criteria for psoriatic arthritis. According to the Moll and Wright criteria, the PsA patients were all presenting with arthritis involving the hand, distal interphalangeal (DIPs), and Tendoachilis at the time of the study. The American College of Rheumatology (ACR) joint count for tenderness and swelling was done. All PsA patients had nail changes in the form of nail pitting and ridging. Patients` were neither receiving treatment for Ps nor for arthritis at the time of the study. No topical treatment for one month before the study.

All patients and controls were subjected to the following: Assessment of Rheumatoid factor for CASPAR Criteria, serum TNF alpha and PEDF: performed by Enzyme-Linked Immune Sorbent Assay (ELISA).

Calculation of Ps Area and Severity Index (PASI score): The head (H) represents 10% of a person's skin, followed by the arms (20%), the trunk (30%), and the legs (L) (40%) of the body. Each of these categories is scored independently, and the four results are then added together to create the total PASI. A grade from 0 to 6 is created for each section based on an estimate of the percentage of skin area affected. Three clinical indicators are used to determine the severity of each area: erythema (redness), induration (thickness), and desquamation (scaling). Severity parameters are rated on a scale of 0 to 4, with 4 being the highest severity. For each portion of skin, the sum of the three severity criteria is then calculated, multiplied by the area score for that region, and multiplied by the weight of the respective section (head: 0.1, arms: 0.2, body: 0.3, leg: 0.4).

Ethical Approval: Al-Azhar University Ethics Board approved the study, and the patients received all the information they required regarding the trial. Each study participant signed written consent after receiving full information. The Declaration of Helsinki, the code of ethics of the World Medical Association, was followed when conducting this research on humans.

Statistical analysis

Statistical Package for Social Sciences was used for data analysis (version 21; SPSS Inc., Chicago, IL, USA). Data were presented as mean, standard deviation, and percentages. For group comparison, the independent t test, Mann Whitney test, and chi-square test were utilised. P-values ≤ 0.05 were regarded as significant.

RESULTS

Demography of the studied groups: This case-control study included 60 patients (30 patients with Ps & 30 PsA patients). Their ages ranged from 20 to 50 years (mean of 33.25 ± 8.58 years). They were 34 males (35%) & 26 females (65%). Besides, thirty controls were included in the study. Their ages ranged from 21 to 42 years (mean of 32.05 ± 6.04 years). They were 13 males (43%) and 17 females (56.6%)**.**
Regarding age (years) and sex, no statistically significant difference between the studied groups was found (P value = 0.519).

Descriptive clinical data of patients: The duration of the disease ranged from 1 year to 20 years with a mean of 6.45 ± 5.87 years in Ps patients & between 6 m to 5 years in PsA with a mean of 2.43 ± 1.75 years. PASI score ranged from 2.1 to 26.7 in Ps with a mean of 13.06 ± 7.94, and from 12.4 to 45.2 in PsA with a mean of 28.8 ± 4.74. The age of onset of disease ranged from 18-42 years in Ps with a mean of 26.75 ± 8.14 years and from 32.4 to 45 in PsA with a mean of 16.72 ± 6.13. Six psoriatic patients had a positive family history of Ps representing 20 % and seven of PsA patients (23%). There was no statistically significant difference (P value=0.742) between male and female patients as regards PASI score**.**
Statistically significant increase in TNF and decrease in PEDF levels were found between patients and control p = 0.001 with a higher significant difference p =0.000 in PsA patients as shown in table (1).

Table (1): Comparison between TNF-α level & PEDF level in both patients and control by chi-square test

	Patients with Psoriasis (N=30)	**Patients with Psoriatic Arthritis (N=30)**	**Control (N=30)**
	Mean±SD	**Mean± SD**	**Mean ± SD**
TNF-α (ng/dl)	240.7 ±19.8	513.7± 13.6	101.52±5.16
PEDF (µg/dl)	90.68±5.21	116.1±6.3	173.53± 6.7
P value: 0.001* and 0.000* (Significant)			

Statistically significant increase in serum TNF-α level with the severity of both Ps and PsA P= 0.000, Also high statistically significant increase in MD1 and increase the negativity of PSD1 with the severity of both Ps and PsA P= 0.000 as shown in table (2).

Table (2): Correlation between TNF-α and PEDF levels with the disease severity by chi-square test

	Psoriasis			**Psoriatic arthritis**		
Severity	Mild	Moderate	Severe	Mild	Moderate	Severe
TNF	61.28	210.775	509.77	194	494.67	658.5
PEDF	148.53	87.933	22.4975	166.33	127.4	76.767
MD1	-0.348	-2.0475	-13.375	-1.683	-8.53	-19.516
PSD1	6.905	2.2075	1.235	11.83	7.0856	2.514
P value: 0.000* Significant						

Figure (1) showed fundus examination of patient with mild psoriasis

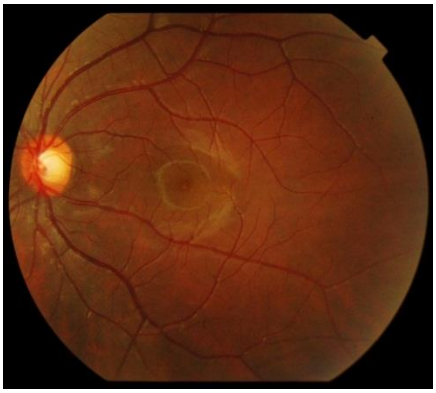

Figure (1): Normal colored fundus in mild Ps.

Figures 2, 3, 4, 5, 6, 7 showed visual field defects in patients with mild, moderate and sever psoriasis**.**

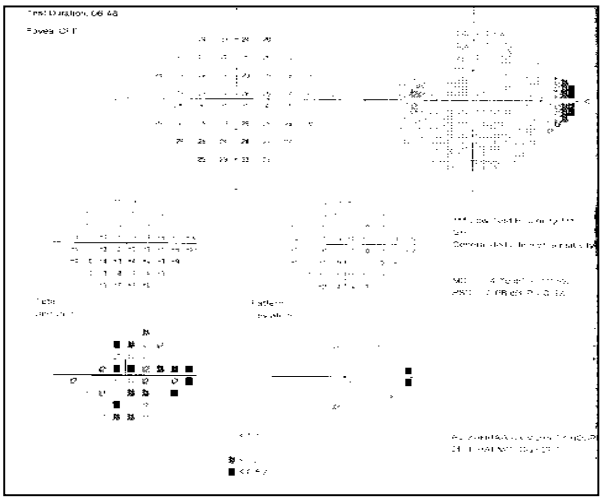

Figure (2): Enlarged blind spot in mild ps.

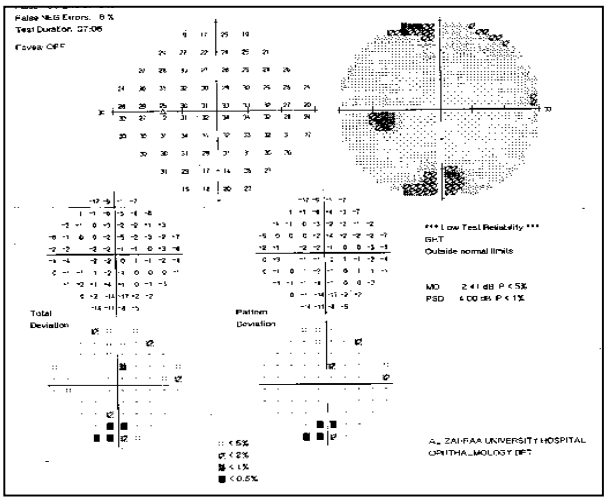

Figure (3): Paracentral scotoma in moderate ps**.**

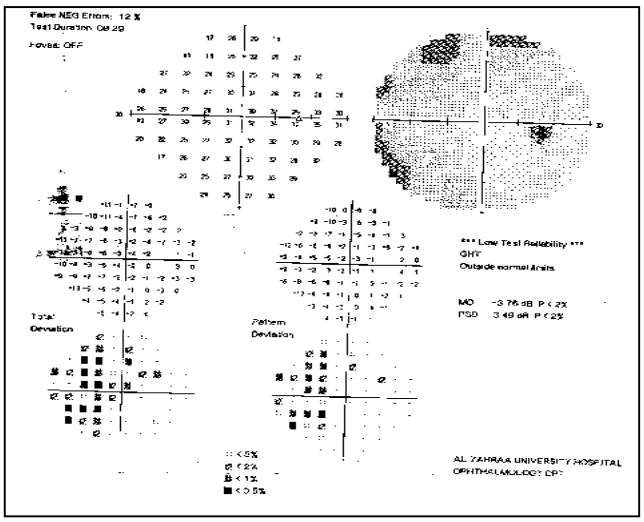

Figure (4): Nasal incomplete hemianopia in server ps.

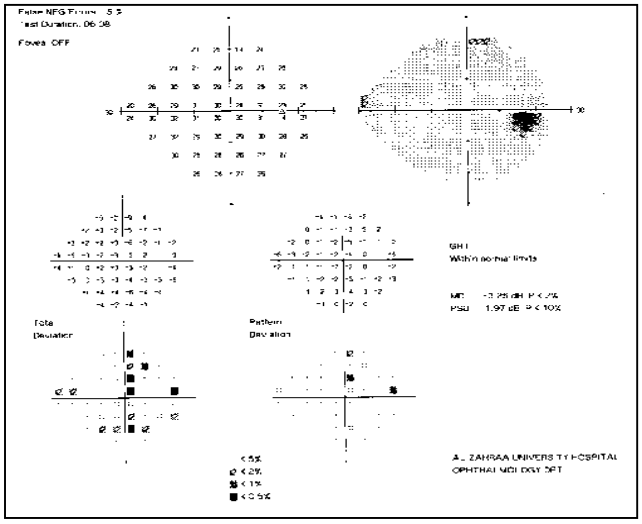

Figure (5): Points of depressed sensitivity in mild ps.

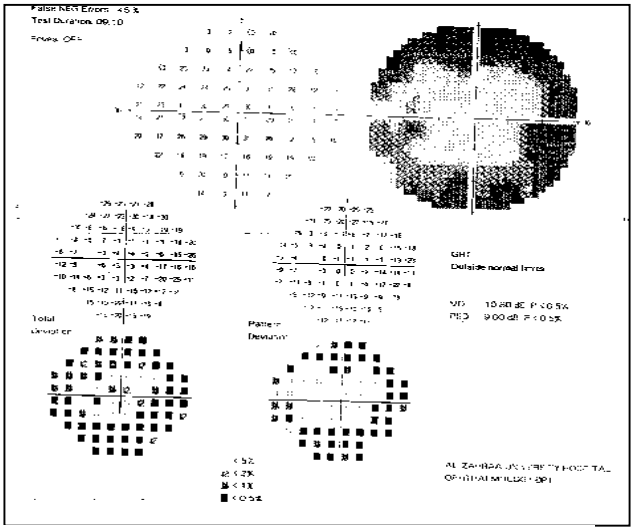

Figure (6): Double arcuate defect in severe ps.

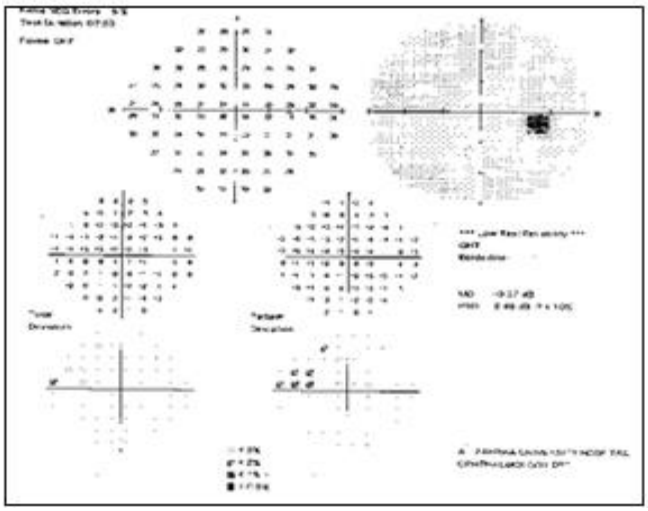

Figure (7): Early upper nasal quadrantic defect in moderate ps..

DISCUSSION

The eye symptoms of Ps can cause a number of issues, including vision loss. Although they have been linked to Ps patients without arthritis, they are more frequently seen in PsA patients [7].

In this case-control study, blood levels of TNF-α and PEDF were measured by ELISA and correlated with visual function in 30 patients with Ps and 30 patients with PsA compared to 30 controls.

Our findings, which agree with those of **Demir *et al.*** [8] who found abnormalities in the visual field in psoriatic patients and controls but were statistically insignificant, showed a statistically significant difference between psoriatic patients and controls in the prevalence of visual function impairment. Their study group included patients with moderate Ps, which could account for the statistically negligible intergroup variation in the visual field characteristics and explain the dispute.

Psoriatic patients' visual field defects ranged from larger blind spots in isolated locations to paracentral scotomas, points of reduced sensitivity, arcuate defects, and quadrant defects. According to our findings, patients with visual field deficits who had psoriasis had greater serum levels of TNF-α than patients without visual field defects. According to **Fotiadou *et al.*** [9] and **Verghese *et al.*** [10], who found considerably higher levels of TNF- α in psoriatic patient compared to controls, the serum level of TNF-α in psoriatic patient in the current investigation was significantly greater than that in controls. Severe Ps had greater TNF-α levels than moderate and mild forms of the disease. In accordance with **Sereflican *et al.*** [11], who found that TNF-α level increased considerably with PASI score and TNF- α level also positively correlates with the severity of Ps according to PASI score. When compared to psoriatic patients and controls, PsA patients' serum levels of TNF alpha were markedly elevated. **Shahin *et al.*** [12] discovered that there was a significant increase, which is consistent with our findings. These findings are in line with those of **Xu *et al.*** [13], who discovered that patients with PsA had higher levels of the pro-inflammatory cytokine TNF-α than psoriatic and healthy controls in the joint synovium and skin lesion. These findings suggested that TNF-α is created and acts locally, and that its levels in the blood may be lower than those in the inflammatory area.

In agreement with **Nakajima *et al.*** [14] who found a significantly greater level of PEDF in psoriatic patients compared to controls and came to the conclusion that circulating PEDF levels were up-regulated in the sera of Ps patients, serum PEDF levels were significantly higher in psoriatic patients. These results imply that PEDF may mediate the anti-inflammatory effects in Ps. Our findings did not agree with those of **Abe *et al.*** [5] who previously found no differences between normal controls and psoriatic patients in terms of the serum levels of PEDF. As in the current study, severe Ps had lower serum levels of PEDF than mild and moderate variants. Also, there was a poor correlation between PEDF serum level and PASI score. Our findings are at odds with those of **Nakajima *et al.*** [14], who claimed that there was a weakly positive association between the PASI score and PEDF level of psoriatic patients. However, there were no appreciable variations in PEDF levels based on the degree of Ps as determined by the PASI score.

TNF-α level in the blood correlated negatively with PEDF level in the blood. That's in line with **Nakajima *et al.*** [14] findings, which although they found a negative association between TNF-α and PEDF levels, they did not find it to be statistically significant. This harmful connection can be deduced from the decrease in PEDF protein expression after TNF-α treatment [15] and the decrease in PEDF mRNA caused by TNF [16]. Our findings may be explained by Ps, which has a complex pathophysiology and a close association with pro-inflammatory cytokines such TNF- α, (IFN-γ) and interleukins 6 and 8 [8]. This may be explained by the fact that nerve cells, which share an embryologic origin with keratinocytes, may be particularly sensitive to the effects of this cytokine because they share some chromosomal anomalies.

TNF-α can both start and encourage the development of nerve dysfunction. TNF- α-induced microvascular damage may result in nerve ischemia and increased vascular permeability, allowing hazardous chemicals to contact nerve fibres. On the other hand, it has been demonstrated that local TNF-α attacks Schwann cells to cause demyelination [17]. Retinal neurons undergo apoptosis as a result of increased TNF-α expression, which results in retinal neurodegenerative diseases. By acting as an upstream regulator, TNF- α has been shown to exert direct and indirect toxicity towards retinal neurons and photoreceptors [18]. According to **Demir *et al.*** [8], the inflammatory response and possibly elevated plasma levels of circulating pro-inflammatory cytokines appear to alter retinal functioning and reduce retinal sensitivity in active and severe Ps.

Patients with moderate and severe Ps were more likely to experience visual impairment than those with mild Ps. Defects in the visual field had a positive correlation with PASI score.

According to **Demir *et al.*** [8], there is a bad association between PASI and MD (mean deviation) of visual field studies. As Ps gets worse, retinal sensitivity seems to decrease. Positive associations between the CPSD (corrected patterns standard deviation), PSD (pattern standard deviation), and PASI may point to localised impairments in the visual field during exacerbation episodes.

When compared to patients with negative visual field defects, psoriatic patients with positive visual field defects had lower serum levels of PEDF. The emergence of proliferative retinopathy's clinical

symptoms was predicted by a low PEDF value. Visual field defects were statistically significant more common in individuals over 30 years of age than in younger patients, which may be related to the substantially higher number of older psoriatic patients.

CONCLUSION

In contrast to psoriatic individuals with negative ocular problems, our investigation revealed higher ophthalmic complications in those with severe psoriasis as indicated by elevated serum TNF-α and decreased serum pigment epithelium derived factor (PEDF) levels.

DECLARATIONS

- **Consent for publication:** I certify that all authors had given their consent to submit the work.
- **Availability of data and material:** Available
- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of interest:** no conflicts of interest.

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