Serum Levels of Plexin B2 in Psoriasis: A case-control study

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Background: Psoriasis is a severe, long-lasting, immune-mediated, hyperproliferative, and inflammatory skin condition that can cause painful or itchy lesions and have a significant impact on quality of life. Psoriasis' complex and poorly understood etiopathogenesis.PlxinB2 has an impact on T-cell morphology that is mediated via CD100. Consequently, they play a function throughout an immune response.

Objectives: Asses serum level of plexin B2 in psoriatic patients& find any possible correlation between serum level of plexin B2 and Psoriasis Area and Severity Index (PASI) score.

Patients and methods: Cross sectional-case control study was carried on psoriatic patients who came to the Dermatology Outpatient Clinic of South Valley University Hospitals. The study started with 50 psoriatic patients& 50 controls healthy individuals unrelated, age, sex, BMI matched with volunteers. The Psoriasis Area and Severity Index score (PASI) used for evaluation of psoriasis vulgaris severity, then serum plexin-b2 level was measured using commercial available ELISA Assay kit .

Results: Regarding patient's age, the 2 groups were matched for age (p=0.064). Likewise, the mean BMI (p = 0.614) sex distribution was comparable in all groups with (p =1.000), there was significantly higher mean of serum Plexin-B2 in cases (10.3 ± 2.3 pg/ml) compared to control (4.3 ± 0.3, p<0.001 pg/ml) (p=0.011), there was significant (<0.001) positive high correlation between s. plexin-b2 and disease severity (r=0.703),

Conclusion: The current work confirming high serum plexin-b2 in psoriasis vulgaris in a high significant manner with the disease severity so, plexin-b2 may have role in psoriasis vulgaris pathogenesis.

Keywords: Psoriasis vulgaris; Plexin-b2;PASI.

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Introduction

Psoriasis is a serious, ongoing, immune-related, hyperproliferative skin condition that also has a significant impact on quality of life. In various nations, the prevalence of the condition ranges from 0.51% to 11.43% **(Michalek et al., 2017.** Although the pathophysiology of psoriasis is not entirely known, genetic, immunological, and other environmental variables might be significant contributors. The pathogenic process comprises of dermal inflammation involving innate and adaptive immune cells and hyperproliferation of keratinocytes **(Ehrin and James, 2016).**

Now, keratinocytes is the most important cause in pathogenesis of psoriasis **(Krueger et al., 2014).** They cause damage-associated molecular pattern molecules, which activate the inflammation, to be produced in psoriasis**(Roney et al., 2013).**

Plexins (PLXN) are trans-membrane proteins act as receptors for semaphorins& interact with CD100 & induce epithelial repair, PlxinB2 has effects T-cell morphology (**Witherden et al., 2012**). Plexins mediate cell to cell interaction & cell movement during inflammatory response **(Holl et al., 2012).**

Psoriasis severity & symptoms can be under control by multiple available lines of treatment but cannot be cured at all **(Kim et al., 2017).** Severe disease is controlled by Systemic therapy, like phototherapy, acitretin, methotrexate, cyclosporine, or biologic therapy **(Kim et al., 2017).**

Patients and methods

Study design and participants

This cross sectional study was carried on 50 patients diagnosed as psoriasis vulgaris who came to the Outpatient Dermatologic Clinic of Qena South Valley University Hospitals,Qena,Egypt & were comparable with 50 age, sex, BMI matched healthy volunteers selected as control,all patients with Pregnancy, lactation, history of any inflammatory diseases as AD, asthma, ulcerative colitis and Crohn's disease & any other similar disease were excluded.

Ethical considerations: Approval for this study was obtained from Institutional review board (IRB) of Faculty of Medicine-Qena University prior to study execution. In addition, all participants received a written consent form. The informed consent was clear and indicated the purpose of the study, and their freedom to participate or withdraw at any time without any obligation. Furthermore, participants' confidentiality and anonymity were assured by assigning each participant with a code number for the purpose of analysis only. The study was not based on any incentives or rewards for the participants. The study was in line with the Declaration of Helsinki. Study was carried on from 9/2021 up to 3/2023. Ethical approval code: SVU,MED,OBG024,4,23/9,733.

Clinical assessment

General examination were done to exclude any associated systemic illness and any similar disease &Local examination were done to evaluate the severity of psoriasis Vulgaris :The Psoriasis Area and Severity Index score (PASI) were be calculated for all patients & categorized as mild (<10) or moderate to severe (≥10**) (Llamas -Velasco et al., 2017),**then venous blood sample 2ml were drained to determine level of plexinb2 level by Human Plexin-B2.

Serum Plexin B2 assays

Two ml venous blood were withdrawn from each participant using serum gel separator tube & blood sample allowed to be clotted 30 minutes at 37^0c then were centrifuged at 3500 rpm for 5 minutes, separated sera were stored at -80^0c till time of plexin b2 assay using commercial available ELISA kit supplied by Chongqing Biopsies co,China with catalog No: BZEK1453-96 based on

standard sandwich enzyme-linked immune-sorbent assay technology, and using microplate ELISA reader (EMR-500,USA), any patient with psoriasis vulgaris were included in our research & patients with Pregnancy, lactation, history of any inflammatory diseases as AD, asthma, ulcerative colitis and Crohn's disease & any other similar disease were excluded.

Statistical analysis

Statistical analysis was conducted using IBM-SPSS ver. 24, categorical variables were presented as frequency and percentages, comparison of proportions between groups was conducted using Chi-square test. Quantitative variables were presented as mean, median, standard deviation (SD), and range. Comparison of quantitative data was conducted using Independent Sample t-test/Mann Whitney U test after normality testing using Shapiro-Wilk test as appropriate. For continuous variables with more than two categories; ANOVA test was calculated to test the mean differences of the data that follow normal distribution and independent, post-hoc test was calculated using Bonferroni corrections. Student t-test was calculated to test the mean differences in continuous variables between groups. A p-value < 0.05 was considered significant, sample size calculated according to:

$$n\,(each\ group) = \frac{(p_0q_0 + p_1q_1)\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2}{(p_1 - p_0)^2}$$

Results

Regarding patient's age, the 2 groups were matched for age (p=0.064). Likewise, the mean BMI (p = 0.614), sex distribution was comparable in all groups with p value of 1.000 as shown in (**Table.1)**.

Table 1. Baseline Demographic Characteristics of the studied groups *Independent Sample

Variables	Control (n = 50)	Cases (n = 50)	P-value
Age/years (Mean ± SD)	41.37 ± 12.1	46.20 ± 13.7	0.064*
Sex			1.000**
• **Male**	30 (60%)	30 (60%)	
• **Female**	20 (40%)	20 (40%)	
BMI (Mean ± SD)	28.31 ± 4.4	27.94 ± 2.8	0.614*

t-test was used to compare the mean difference between groups; **Chi-square test was used to compare frequency between groups

There was significantly higher mean of serum plexin-B2 in cases (10.3 ± 2.3 pg/ml) compared to control (4.3 ± 0.3, p<0.001 pg/ml) (p=0.011), **(Table.2).**

Table 2.Plexin-B2 of the studied groups

Variables	Control (n = 50)	Case (n = 50)	P-value
Serum Plexin-B2 Level(pg/ml)			**= 0.011***
• **Mean ± SD**	4.28 ± 0.3	10.30 ± 2.3	

There was insignificant difference in the mean S.Plexin-B2 level between primary cases (12.6 ± 6.4 pg/ml) compared to recurrant cases (9.7 ± 2.4 pg/ml) (p=0.369) as showed in **(Table.3).**

Table.3. S.Plexin-B$_2$ level according to Recurrence

Variables	Primary (n = 10)	Recurrent (n = 40)	P-value*
Serum Plexin-B2 Level	12.57 ± 6.4	9.73 ± 2.4	0.369

*Independent t-test was used to compare the mean difference between groups

There was statistically significant high mean serum plexin-B2 level was observed in severe cases (14.2 ± 2.9 pg/ml) compared to moderate cases (3.3 ± 1.2 pg/ml)(p=0.004) according to disease Severity by PASI score as showed in **(Table .4).**

Table.4: S.Plexin-B$_2$ level according to disease Severity

Variables	Moderate (n = 18)	Severe (n = 32)	P-value*
Serum Plexin-B2 Level	3.33 ± 1.2	14.22 ± 2.9	**0.004**

*Independent t-test was used to compare the mean difference between groups.

There was significant positive high and high moderate correlation between s. plexin-b2 and disease severity (r=0.703) & (p<0.001). In other words, increase in the level of s. plexin-b2 was associated with higher disease severity; also there was insignificant negative/positive minimal to mild correlation with age, sex, BMI and disease duration as shown in (**Table.5, Fig. 1).**

Table 5.Correlation between Plexin-b2 Level and Basic Correlates.

Variables	S. Plexin-b2 r (p value)
• **Age**	0.106 (0.146) *
• **Sex**	-0.095 (0.175) **
• **BMI**	-0.096 (0.254) *
• **Disease Duration**	-0.104 (0.265) *
• **Disease Severity**	**0.703 (<0.001) ** **

*Pearson's correlation coefficient (PCC) was used for normally distributed data; **Spearman Ranked correlation coefficient (SRC) was used for data not normally distributed

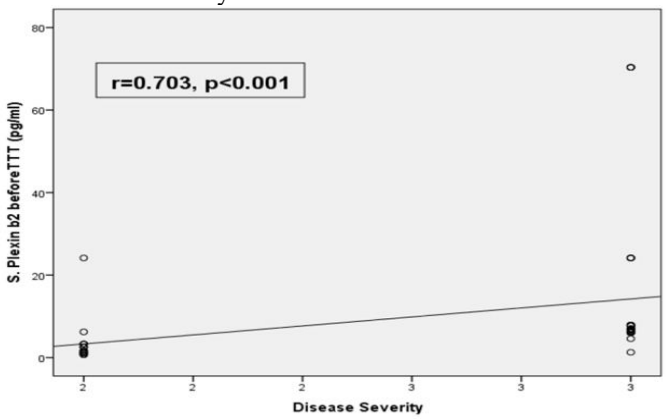

Fig.1. Correlation between S. Plexin Level and Disease Severity

S.plexin-b2 level had good predictive power for disease severity, AUC = 0.922, p = < 0.001; 95% CI: 0.823 - 1.000. Moreover, at ≥4 pg/ml, the validity criteria were as follows; 97%sensitivity, i.e., s. plexin-b2 correctly identified 97% of positive cases as having sever disease. Also, 89% specificity, Additionally, the test had 90% precision -Positive Predictive Value (PPV) i.e., the ability of the test to predict actively diseased patients among all positive cases. It also had 97% Negative Predictive Value (NPV) i.e., the ability to predict those with inactive disease among all those diagnosed as negative and overall, the test had 93% accuracy as shown in **(Table.6, Fig. 2)**.

Table 6. Diagnostic criteria of S.Plexin-b2 for Prediction of Disease Severity

Diagnostic criteria	S. Plexin-b2
• AUC	0.922
• 95% CI	0.823 - 1.000
• P-value***	< 0.001
• Cutoff	≥4 pg/ml
• Accuracy	93%
• Sensitivity%	97%
• Specificity%	89%
• PPV%	90%
• NPV%	97%

*AUC=Area under the Curve **SE=Standard Error CI=Confidence Interval ***Null hypothesis: true area=0.5; Sensitivity (true positives/all diseased); specificity (true negatives/all non-diseased); PPV (true positives/all test positives); NPV (true negatives/all test negatives).

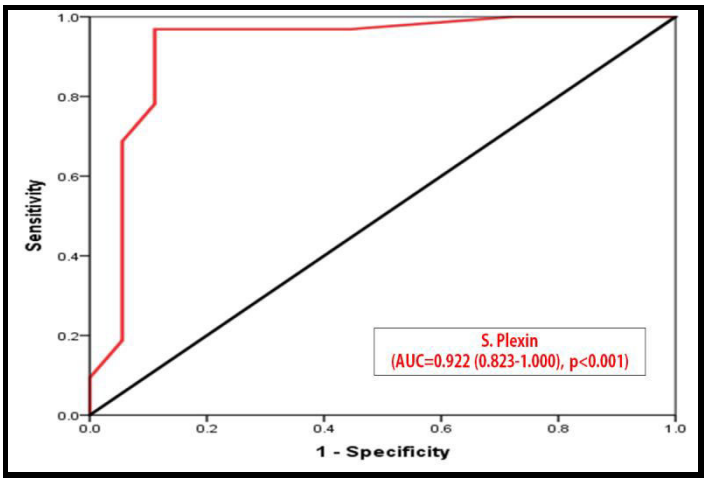

Fig. 2. ROC Analysis of S. Plexin-B2 Level for Prediction of Disease Severity.

Discussion

In our study, Regarding patient's age, the 2 groups were matched for age (p=0.064). Likewise, the mean BMI (p = 0.614), sex distribution was comparable in all groups with (p =1.000). **(Napolitano et al., 2020)** found sex- and gender-associated differences in clinical characteristics, disease severity, psychological distress and quality of life as female sex was associated with higher psychological distress and a greater effect on quality of life.

(Guillet et al., 2022) agreed with our study and found se xes not affect incidence, prevalence, and manifestation of psoriasis, but not totally agreed with us as he found disease severity & impairment of quality of life less in female compared with male& women are more likely to manifest depression than men **&(Gupta et al., 1995)** agreed with our study and found no age or gender differences in the severity of psoriasis were observed,(**Alamri et al., 2022)** not agreed with our study and found that psoriasis caused a significant impairment in the quality of life in female patients compared to males **(Fleming et al., 2015**) agreed with our study and found that no significant difference between mean value of body mass index, waist size, age and gender in mild, moderate and severe groups of the psoriasis patients.

In our results, serum plexin-B2 level, significantly higher mean was observed in cases (10.3 ± 2.3 pg/ml) compared to control (4.3 ± 0.3, p<0.001 pg/ml) (p=0.011) and this was statistically significant (p<0.001).There was significant (<0.001) positive high and high moderate correlation between s. plexin-b2 and disease severity (r=0.703). In other words, increase in the level of s. plexin-b2 was associated with higher disease severity.

(Hemida et al., 2020) agreed with our study and found that psoriasis severity correlated positively to of Plexin-B2 expression and (r = 0.557; P < .001), **(Zhang et al., 2018**) backed up our study's findings, which showed that (CD100) levels in psoriasis patients' serum and keratinocytes on psoriatic skin had dramatically increased. (**Wang et al., 2001)** supported our research and discovered that CD100 is the most well-known ligand for PlxnB2. The sera of autoimmune-prone mice contain a significant quantity of sCD100**. (Witherden et al., 2012)** revealed that dermal inflammatory cells in lesional skin of psoriasis patients significantly expressed Plexin-B2 more than controls skin. Plexin-B2 is detected in mouse keratinocytes and is involved in keratinocyte proliferation and the repair process in wound healing.**(Kolodkin , 1996)** described roles of Plexin-B2 in T cell priming, antibody production, and cell-to-cell adhesion, **(Yan et al., 2017)** examined the link between plexin-b2 and its receptor, CD100, can activate T cells, and how plexin-b2 increases inflammation in psoriasis lesions. **(Yan et al., 2017**) discovered that T-cell activity and recruitment in the germinal center related to PlxnB2 and CD100 . **(Besliu et al., 2011)** discussed the role of plexin-b2 in sera of other inflammatory disease systemic sclerosis and (**Yoshida et al., 2015**) found that plexin b2 increased significantly in the sera of rheumatoid arthritis patients .

To the best of our knowledge it's the first study to validate the serum level of plexin-b2 in psoriasis severity that could be helpful with clinical correlation; we found that serum plexin-b2 at cut off ≥4 pg/ml, the validity criteria were as follows; 97%sensitivity, i.e., s. plexin-b2 correctly identified 97% of positive cases as having sever disease. Also, 89% specificity, Additionally, the test had 90% precision - Positive Predictive Value (PPV) i.e., the ability of the test to predict actively diseased patients among all positive cases. It also had 97% Negative Predictive Value (NPV) i.e., the ability to predict those with inactive disease among all those diagnosed as negative and overall, the test had 93% accuracy.

Study limitations: The main limitation of this study:Small number of our cases.We did not account for other clinical factors associated with serum Plexin –B2 levels variations. Other causes of variations in Plexin –B2 not considered. We assessed serum Plexin –B2 levels in one area and

government. We used the PASI score to evaluate Psoriasis vulgaris severity only& the PASI has been criticized as not correlating the clinical extent of the disease with quality of life and the psychological stress caused by psoriasis also some severe disease (clinically) may be scored low. For example, scores as low as 3 (on palms and soles) may represent psoriasis that disables a patient from work and other life activities.

Conclusion

In this study, plexin-b2 may have role in pathogenesis of psoriasis particularly in sever type.

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