Correlation Between Interleukin-19 Concentration And Acne Vulgaris

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Background: Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit. Ductal hyperkeratinization, increased secretion of sebum, and colonization of Propionibacterium Acnes (P. acnes) around the pilosebaceous gland are among the factors responsible for the etiopathogenesis of acne vulgaris. Interleukin-19 (IL-19) is a cytokine expressed by epithelial cells with proinflammatory stimulation. A distinctive feature of IL-19 is their ability of giving positive feedback loop to amplify themselves; once they are activated in inflammatory process, they will continuously produce the cytokine. The study aimed to identify the relation between blood levels of IL-19 and acne vulgaris.

Methods: 36 acne patients and 12 healthy subjects were included in our study. All of patients and controls were subjected to full history, full general and dermatological examination. Serum IL-19 level was measured from each subject using quantitative sandwich enzyme-linked immunosorbent assay (ELISA) serum kits.

Results: There was no statistical significance difference between the cases and controls in age and sex. Serum Interleukin 19 level is highly significant increased in patients with acne compared to controls. Serum IL-19 level was statistically significant with age of patients, disease duration and site of lesion.

Conclusion: Interleukin 19 is higher in acne compared to controls. level of IL-19 positively correlated with age of patients and disease duration, that was statistically significant.

Key words: Interleukin-19 - Acne Vulgaris - Evaluation-

1. INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit. Ductal hyperkeratinization, increased secretion of sebum, and colonization of Propionibacterium Acnes (P. acnes) around the pilosebaceous gland are among the factors responsible for the etiopathogenesis of acne vulgaris\textsuperscript{(1)}. It is a popular skin disease with the incidence in adolescence of up to 85\textendash 100\%, including 30\% moderate and 10\% severe acne\textsuperscript{(2)}. It is estimated that 9.4\% of the world’s population is affected by acne vulgaris (AV) with the highest prevalence among adolescents\textsuperscript{(3)}. It is ranked as the eighth most common disease worldwide\textsuperscript{(4)}.

Propionibacterium acnes (p. acnes) is responsible for the local tissue inflammatory reactions of acne. These initiate an innate immunity via activation of Toll-like receptor (TLR)-2 and TLR-4. It stimulates different pathways that eventually activate the transcription factor nuclear factor (NF)-kB.
This in turn triggers release of various inflammatory mediators such as IL-6, IL-8, IL-10 and tumour necrotic factor-a. IL-6, along with other inflammatory cytokines, can stimulate the T-helper (Th)17 axis of the adaptive immune response, which contributes to the inflammatory reaction in acne\(^\text{(5)}\).

Colonization of the pilosebaceous follicle by P. acnes is considered as one of the central factors driving acne by taking part in the inflammatory response of the skin, in addition to the cutaneous microbiota and innate immunity. Two other factors involved in this chronic inflammatory skin disease are the increased sebum production, with a modification of its composition, and hypercornification of the pilosebaceous follicle resulting from hyperproliferation and abnormal differentiation of keratinocytes of the upper part of the follicle\(^\text{(1)}\).

Recent study showed that inflammation does have a central role in the formation of both inflammatory and noninflammatory lesions in acne vulgaris. The inflammation in acne vulgaris itself linked with P. acnes. Propionibacterium acnes stimulates keratinocytes through the Toll-like receptors (TLRs) to produce proinflammatory cytokines. An example of proinflammatory cytokines that are already known is interleukin- (IL-) \(1\)\(^\beta\). The other cytokines related to pathogenesis of acne vulgaris are IL-6, IL-8, IL-10, and IL-12\(^\text{(6)}\).

Interleukin- (IL-) 19 is a cytokine expressed by epithelial cells with proinflammatory stimulation. A distinctive feature of IL-19 is their ability of giving positive feedback loop to amplify themselves; once they are activated in inflammatory process, they will continuously produce the cytokine\(^\text{(6)}\).

The study aimed to identify the relation between blood levels of IL-19 and acne vulgaris.

### 2. PATIENTS AND METHODS

I) **Technical design:**

1. **Site of study:** out-patient clinic of Dermatology, Venereology and Andrology Department at Zagazig University Hospitals.
2. **Sample Size:** assuming that mean ± SD of IL-19 concentration in mild acne vulgaris is 18.38 ± 9.59 versus 31.19 ± 20.36 in severe acne vulgaris so the sample size is 48 (36 patients and 12 controls) using OPEN EPI at power 80% and C.I 95%.
3. **Subjects included in the study:**

   **Patients:**

   The study included 48 individual divided into 2 groups: Patient group: 36 patients with acne vulgaris. Control group: 12 healthy persons were enrolled to assay serum level of Interleukin-19 using ELISA kits.

   **Inclusion criteria:**

   - Include subjects between the ages of 16 and 30 years.
   - Clinical cases diagnosed with acne vulgaris who were willing to participate in the research and to fill in a questionnaire and a statement of willingness.
   - Acne vulgaris patients didn't take any systemic or topical treatment in the last two weeks.

   **Exclusion criteria:**

   - Acne vulgaris patients undergoing systemic and topical treatment in the last two weeks.
   - Other conditions that IL-19 plays a role in their pathogenesis such as psoriasis, atopic dermatitis and asthma.

II) **Operational design:**
Type of study: case control study.

METHODS

- The number of samples was determined using unpaired numerical analytical test.
- Informed consents were taken from patients and controls before starting the work.

All subjects in this study were subjected to the following:

1. Detailed history taking:
   - Personal history: name, age, and gender.
   - Present history: onset, course, duration of acne and aggravating factors.
2. Laboratory examination:
   A five milliliters of venous blood sample were collected from each subject in clot activator and gel containing tubes for serum separation for an examination of IL-19 serum concentration. The blood samples were centrifuged at 3000 rpm (CENTRIC 322A® centrifuge) for 15 minutes to separate the serum then stored at -20°C before assaying. Such procedures which applied human IL-19 immunoassay was done by using a double antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Human Interleukin 19 (IL-19) in samples.

III) Administrative design:
- Approval was obtained from Zagazig University Institutional Review Board (IRB).

3. STATISTICAL ANALYSIS

Data were analyzed using IBM SPSS 23.0 for windows (SPSS Inc., Chicago, IL, USA) and NCSS 11 for windows (NCSS LCC., Kaysville, UT, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:
- Independent sample t-test of significance was used when comparing between two means.
- Mann-whitney test was used when comparing two means of not normally distributed data.
- Pearson’s correlation coefficient (r) test was used for correlating continuous data.
- Probability (P-value): P-value ≤0.05 was considered significant, P-value ≤0.001 was considered as highly significant and P-value >0.05 was considered insignificant.

4. RESULTS

- This table shows that there was no statistical significant difference among both studied groups as regarding age, gender and occupation Table (1).
- The mean of Age of onset of disease 16.9 years ranged from 13 years up to 25 years. And the mean of disease duration 24.4 months ranged from 2 weeks up to 96 months Table (2).
- Table (3) and figure (1) show a statistical significant increase of IL-19 among cases than their controls.
- This table shows that level of IL-19 positively correlated with age of patients and disease duration that was statistically significant Table (4).
Table (1): Demographic characteristics among both studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>t-test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=36</td>
<td>N=12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age\ yrs Mean ±SD</td>
<td>18.9 ± 2.91</td>
<td>19.9 ± 3.32</td>
<td>0.97</td>
<td>0.35</td>
</tr>
<tr>
<td>Range</td>
<td>16 - 25</td>
<td>17 - 30</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>Fisher</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>3</td>
<td>X²</td>
<td>0.38</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>9</td>
<td>P value</td>
<td>NS</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>28</td>
<td>9</td>
<td>3.68</td>
<td>0.159</td>
</tr>
<tr>
<td>Nurse</td>
<td>5</td>
<td>0</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS: P-value>0.05 is not significant

Table (2): Clinical data and disease history among studied cases:

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>N=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of onset of disease (years):</td>
<td>16.9 ± 2.57</td>
<td>13 – 25</td>
</tr>
<tr>
<td>Disease duration (months):</td>
<td>24.4 ± 22.6</td>
<td>2 weeks – 96 months</td>
</tr>
</tbody>
</table>

Table (3): Laboratory biomarkers among both studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>t-test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=36</td>
<td>N=12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-19 (pg/ml)</td>
<td>211.6 ± 61.1</td>
<td>20.9 ± 4.98</td>
<td>10.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>57.8 – 369.66</td>
<td>12 – 26.4</td>
<td></td>
<td>HS</td>
</tr>
</tbody>
</table>

S: P-value<0.05 is significant
Table (4): Correlation between IL-19 level with clinical and laboratory data of studied cases.

<table>
<thead>
<tr>
<th>Variables</th>
<th>IL-19</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.394</td>
<td>0.04 S</td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.445</td>
<td>0.02 S</td>
<td></td>
</tr>
<tr>
<td>Age of disease onset</td>
<td>0.177</td>
<td>0.502 NS</td>
<td></td>
</tr>
</tbody>
</table>

NS: P-value>0.05 is not significant
S: P-value <0.05 is significant

5. DISCUSSION

Our study included 48 subjects, divided into 2 groups (patients and control subjects). 36 patients matched with 12 healthy control for age and sex. Serum IL-19 level was measured in each subject using quantitative sandwich enzyme-linked immunoassay assay (ELISA) serum kits (Bioassay Technology Laboratory®/China). Mean age of the control group is 19.9 ± 3.32 year while in cases group it was 18.9 ± 2.91 years. Results revealed that there is no statistical significance difference between the two groups in age distribution nor occupation. Regarding sex about 61.1% of cases and about 75% control are females with no statistical significance difference between the two groups.

The present study show that serum Interleukin 19 level is highly significant increase in patients with acne compared to controls (P <0.001), the mean serum level of IL19 (pg/mL), using ELISA assays, among patients and controls were 211±61.1 and 20.9±4.98 respectively. This higher serum level in acne vulgaris patients could be explained by the fact that Interleukin-19 is a cytokine expressed by epithelial cells under proinflammatory stimulation Fielding. (7).

Propionibacterium acnes that proliferate in the lipid-rich environment contribute to the formation of acne inflammation, by inducing TLR-2 to release proinflammatory cytokines such as IL-1β (8).
The study by Kunz et al. (9) stated that IL-1β could induce expression of IL-19 in keratinocytes both in vitro and in vivo and was supported by Bao et al. (10) who stated that the release of proinflammatory IL-1β leads to the release of IL-19 despite the unknown special activation signal between IL-1β and IL-19. Such cytokines end up with inflammatory processes and tissue damage in acne vulgaris patients with a possibility of an increase in incidence and severity of acne vulgarics. Therefore, such cytokines may relate and influence the degrees of severity of acne vulgaris (11).

Our study showed that, serum IL-19 level was statistically significant with age of patients, disease duration and site of lesion.

6. CONCLUSION
Serum Interleukin 19 level is highly significant increased in patients with acne compared to controls. Serum IL-19 level was statistically significant with age of patients, disease duration and site of lesion.

REFERENCES