Analysis of Inflammatory Cytokine Levels in Sinonasal Secretions of Gulf War Veterans With and without Gulf War Illness

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Introduction

- Gulf War Illness (GWI) is a chronic, multi-systemic disease that has been reported to impact one third of Veterans from the Persian Gulf War (1990-1991).
- Symptoms of chronic rhinosinusitis (CRS), including nasal congestion and fatigue, have been identified as the first (47%) and third (41%) most common complaints associated with GWI. Although the precise etiology is unknown, chronic inflammation has been postulated to contribute to its pathogenesis.
- The purpose of this study was to compare inflammatory cytokine levels of sinonasal secretions from Gulf War Veterans (GWV) with and without GWI associated CRS.

Methods and Materials

- Sinonasal secretions were collected from:
  - Group 1: 11 GWV without GWI associated CRS
  - Group 2: 13 GWV with GWI associated CRS
  - Group 3: 4 patients without GW exposures or CRS
  - Group 4: 4 patients without GW exposures but with CRS
- A standard panel to measure 38 chemokines and cytokines was used to analyze and compare the levels of these immune response markers across various groups.
- Comparisons were made between groups, specifically examining:
  - Group 1 vs Group 2: GWV with and without GWI associated CRS
  - Group 2 vs Group 4: CRS patients with and without Gulf War exposures
  - Group 1 vs Group 3: Patients with and without Gulf War exposures and no CRS
- Cytokines with significant differences were reported in figures 1-3.
- Mann-Whitney test was used with a significance value of 0.05.

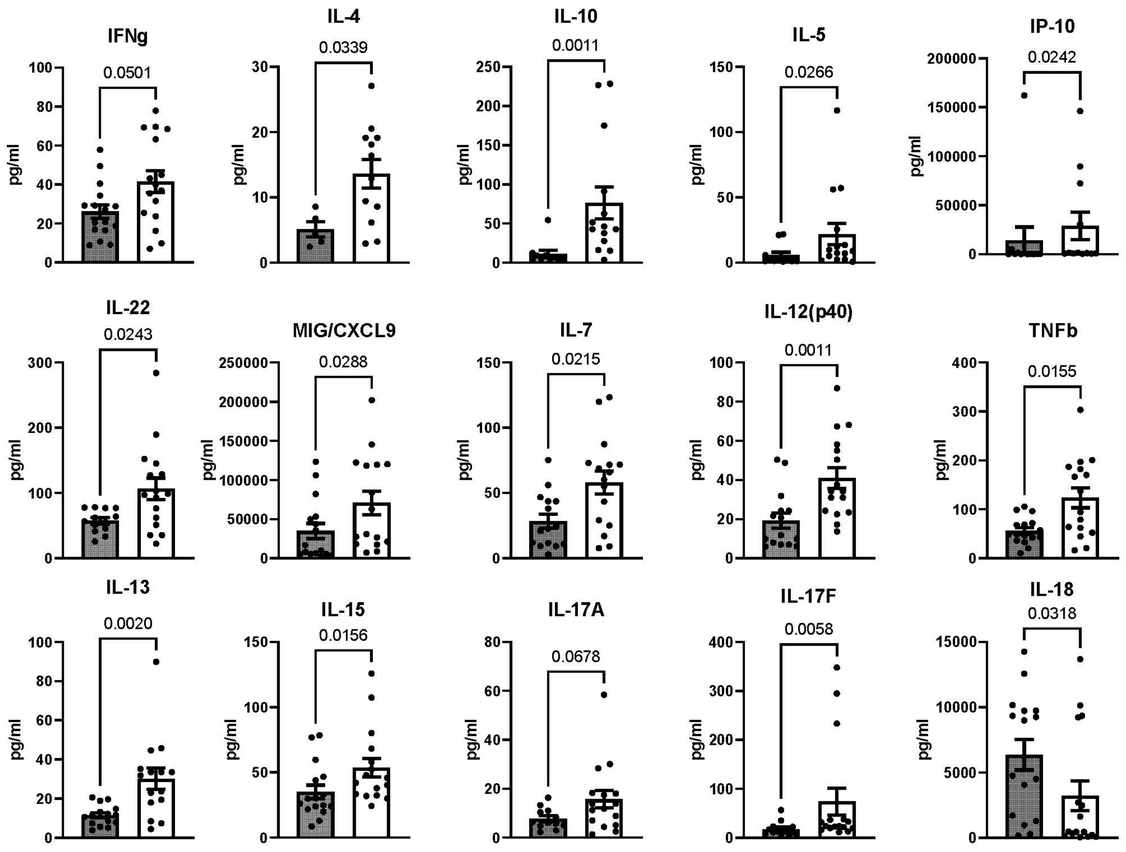

Figure 1 – Pro-inflammatory cytokines gamma-IFN, IL-4, IL-5, IL-7, IL-10. IL-12, IL-13, IL-15, IL-17F, IL-22, TNFb, MIG/CXCL9, and IP-10 in Group 1 (shaded) and Group 2 (clear).

Results

- Patients with GWV with GWI (group 2), when compared to GWV without GWI (group 1), had significantly higher levels of the pro- inflammatory cytokines gamma-IFN, IL-4, IL-5, IL-7, IL-10, IL-12, IL-13, IL-15, IL-17F, IL-22, TNFb, MIG/CXCL9, and IP-10 (Fig. 1) ($p \leq 0.05$). Significantly lower IL-18 levels were observed in GWV with GWI.
- When comparing GWV with GWI associated CRS (group 2) to non-GWV with CRS (group 4), there were significantly higher levels of MCP1, IL-4, IL-10, IL-17F, IL-22, TNFb, M-CSF, and IP-10 in GWI patients (Fig. 2).
- When comparing non-GWV without CRS (group 3) to GWV without GWI/CRS (group 1), GWV had significantly higher IL-10 but lower CSF levels ($p<0.05$).

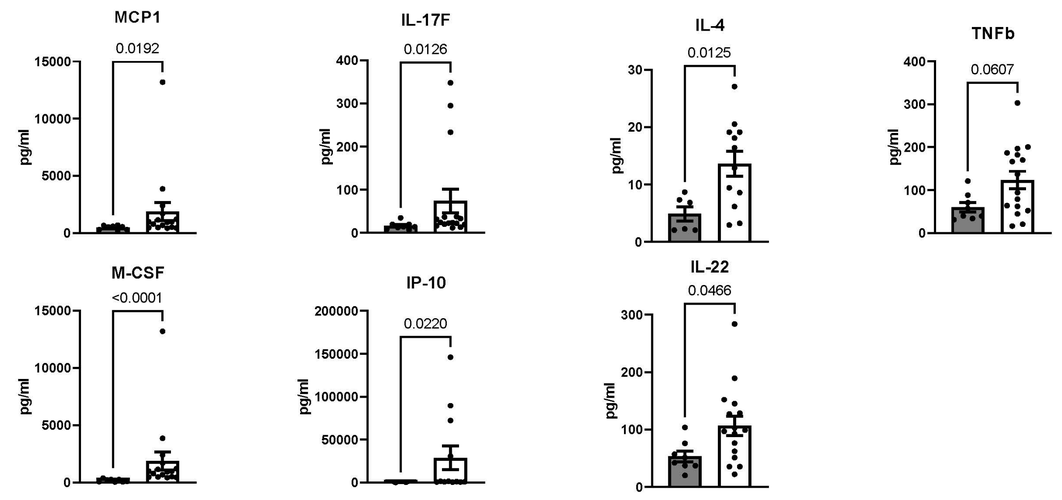

Figure 2 – Pro inflammatory cytokines MCP1, IL-4, IL-10, IL-17F, IL-22, TNFb, M-CSF, and IP-10 in Group 2 (clear) to Group 4 (shaded).

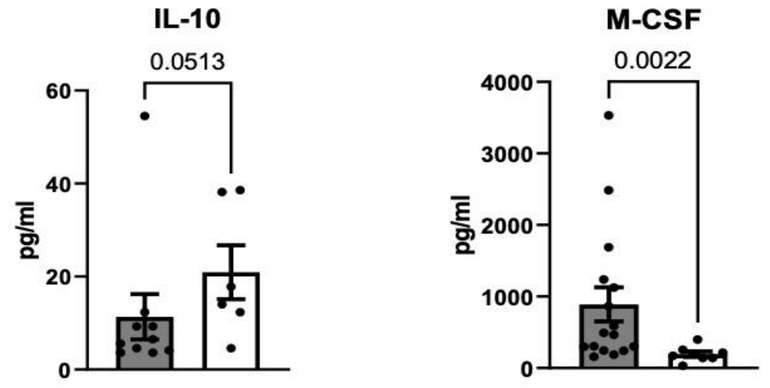

Figure 3 – Pro-inflammatory cytokines IL-10 and M-CSF in Group 1 (clear) and Group 3 (shaded).

Discussion

- Pro-inflammatory cytokines gamma-IFN, IL-4, IL-5, IL-7, IL-10, IL-12, IL-13, IL-15, IL-17F, IL-22, TNFb, MIG/CXCL9, and IP-10 play a significant role in the pathogenesis of GWI in GWV patients.
- Findings from GWV patients with GWI associated CRS compared to non-GWV with CRS indicate that GWI associated CRS is characterized by a more severe inflammatory response than what could be attributed to CRS alone.
- Findings from GWV without GWI/CRS and non-GWV without CRS suggest that GW exposures alone may alter the sinonasal milieu even without manifestation of GWI (Fig. 3).

Limitation: Our study was observational rather than experimental, as cytokine profiles of subjects could not be randomized or manipulated. Accordingly, We are limited to concluding associations, not causation. It is also important to note that our sample was drawn from Southern California; therefore, our results should be considered with caution when applied to different geographic populations.

Conclusions

- To the best of our knowledge, this pilot study is the first to demonstrate differences in inflammatory signatures of the sinonasal milieu in GWV with and without GWI and is consistent with the hypothesis that chronic inflammation contributes to the underlying pathophysiology of GWI.

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