CYTOKINE SIGNATURE DIFFERENCES IN MAJOR PHENOTYPIC GROUPS OF BEHÇET'S DISEASE

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Objectives: Behçet's disease (BD) has heterogeneous presentations, mainly mucocutaneous, vascular, and ocular manifestations. The mechanisms associated with different phenotypes have not been clarified. We aimed to investigate the expression of innate and adaptive immunity-related cytokines in these three main BD phenotypes in active, and untreated states and remission after treatment to be able to develop a cytokine-based treatment algorithm.

Methods: Serum samples were isolated from 41 patients with newly-diagnosed active-BD (aBD), which consisted of 19 mucocutaneous-aBD (m-aBD), 11 ocular-aBD (o-aBD), and 11 vascular-aBD (v-aBD) patients, 35 patients in remission (rBD), and 9 healthy controls (HC). Serum levels of each cytokine were measured with sandwich ELISA and analyzed as both raw measurements and corrected levels for each one million white blood cells.

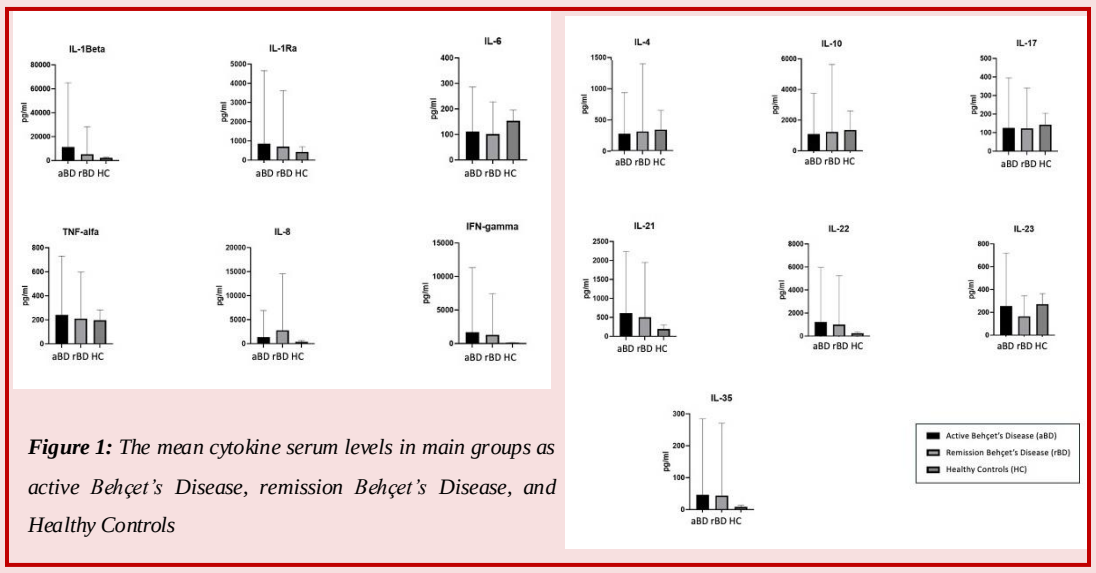

Figure 1: *The mean cytokine serum levels in main groups as active Behçet's Disease, remission Behçet's Disease, and Healthy Controls*

Results: The study included 41 aBD patients (F/M: 9/32, median age 29), 35 rBD patients (F/M: 9/26, median age 29), and 9 HC (F/M: 3/6, median age 28). The serum IFN-gamma level was significantly higher in the aBD group than in the rBD (116 vs 92 pg/ml, p=0.022). The serum IL-35 level was significantly higher in the HC group compared to aBD and rBD (p=0.05). IL-17-related cytokines were lower in o-aBD. With treatment, they increased in o-aBD but decreased in m-aBD and v-aBD patients.

The levels of IL-4 and IL-10 were higher in the HC group compared to the aBD and rBD groups; these levels increased after the treatment in the overall patient group and the phenotypic BD subgroups.

Th17-related cytokines, namely IL-17, IL-21, IL-22, and IL-23, were not significantly different between BD patients with active disease or those in remission, but the levels tended to be higher in the active group. However, in the phenotypic subgroup analysis, the o-aBD group showed the lowest levels of all four cytokines compared to other active subgroups, and there was a tendency to increase after the treatment in the o-rBD group, despite a tendency to decrease in the m-rBD and v-rBD groups.

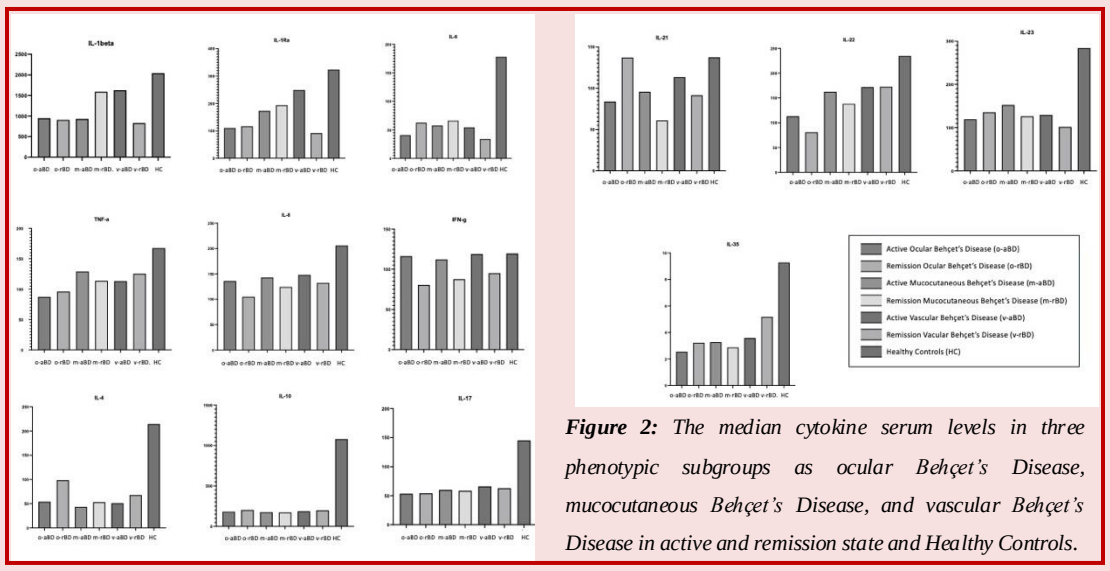

Figure 2: *The median cytokine serum levels in three phenotypic subgroups as ocular Behçet's Disease, mucocutaneous Behçet's Disease, and vascular Behçet's Disease in active and remission state and Healthy Controls.*

Figure 2 shows the differences in cytokine levels between each BD subgroup's active and remission states and HC. Although no significant difference were observed, there were variations in serum cytokine levels between phenotypic subgroups and changes after treatment in individual phenotypic subgroups.

The median cytokine levels in the HC group were higher for all cytokines compared to the active and remission disease subgroups. In the analysis of overall active BD, remission BD, and HC groups, higher cytokine levels were found in the HC group compared to the patient groups. A comparison of the mean values between aBD, rBD, and HC groups showed higher levels of IL-1beta, IL-1Ra, TNF-alpha, IFN-gamma, IL-21, IL-22, and IL-35 in the aBD group compared to the HC group.

Conclusion: We showed that both innate and Th1-related adaptive immunity dominated the immune response in all BD phenotypes, and IL-17-related cytokines were less significantly involved in the immune profile of ocular involvement. These findings confirm the possible differences between phenotypic subgroups and support the development of a phenotype-based treatment algorithm.

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