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Immunoglobulin E: a new diagnostic clue for Behçet's disease? IgE and Behçet's disease

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Abstract Behçet's disease (BD) is a multisystemic inflammatory disorder of unknown etiology. Hyperimmunoglobulinemia has been demonstrated in BD; however, its clinical importance has not yet been discovered. In a few reports, an association between BD and plasma immunoglobulin E (IgE) has been noted. In this study, we had three objectives: (1) to investigate plasma levels of IgE and their association with levels of acute phase reactants, (2) to determine whether treatment has any effect upon IgE levels, and (3) to assess whether higher serum levels of IgE provide a clue for the diagnosis of BD. Fifty-two patients with BD, without any accompanying disease or condition that might lead to a rise in IgE, were compared with 51 age-matched healthy controls. Plasma levels of IgE, IgA, IgG, and IgM were analyzed by means of nephelometric analysis. Results showed that among the 52 patients, 23 (44%) had IgE levels that were higher than the upper limits of normal. IgE was not correlated with age, erythrocyte

sedimentation rate, or C-reactive protein ($p=0.59$, $p=0.57$, and $p=0.757$, respectively). These relationships remained nonsignificant when multiple regression analysis was performed, with R^2 of 0.187 and $p=0.057$. Moreover, treatment of patients with elevated IgE did not produce any predictable IgE response. We conclude that Behçet's patients commonly exhibit elevated plasma IgE levels. However, elevated IgE levels are not correlated with levels of acute phase reactants or disease activity. We suggest that IgE levels might be an independent diagnostic clue in Behçet's patients.

Keywords Acute phase response · Behçet's disease · Immunoglobulin E (IgE)

Introduction

Behçet's disease (BD) is a multisystemic inflammatory disorder that includes recurrent oral aphthous ulcers and at least two of the following features: recurrent genital ulcers, eye lesions, skin lesions, or a positive pathergy test. It has a relatively high prevalence among Turkish people [1]. The pathogenesis and etiology of BD remain unknown. Hyperimmunoglobulinemia has been demonstrated in BD; however, its clinical importance has not yet been discovered [2]. In a few reports, an association between BD and elevated plasma IgE has been noted [3, 4]. In this study, we had three primary objectives: (1) to investigate systemic levels of IgE and their association with levels of acute phase reactants, (2) to determine whether treatment has any effect upon IgE levels, and (3) to assess whether higher serum levels of IgE provide a clue for the diagnosis of BD.

Materials and methods

Subjects and study protocol

Fifty-two patients with BD (31 taking medication for BD, and 21 newly diagnosed and untreated patients) and 51

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age-matched, healthy controls were included in this study. All patients and controls provided informed consent to participate, in accordance with the ethical principles for human investigations, as outlined in the Second Helsinki Declaration. A complete medical history and a physical examination were recorded and performed for each subject, and each patient underwent tests for routine biochemical and hematological monitoring. Plasma IgE, IgG, IgM, IgA, CRP (C-reactive protein), and ESR (erythrocyte sedimentation rate) were analyzed for each patient. Results of peripheral blood smear and microscopic stool examination were also analyzed, the latter performed at least three times for each patient having high IgE levels so as to rule out parasitic disease. Blood samples were drawn from large antecubital veins. All venipunctures were carried out without interruption of venous flow and using a 19-gauge butterfly needle connected to a plastic syringe. All samples were immediately transferred to the laboratory and studied for the above-mentioned variables. Patients and controls having any accompanying disease, or otherwise having any condition that might lead to a rise in plasma IgE levels, having increased eosinophil count either by blood count or peripheral blood smear, or having any parasitic infection were excluded.

Assay

CRP and immunoglobulins were measured by means of nephelometric analysis (NA Latex CRP Reagent: Behring Institute, Marburg, Germany); the normal range for CRP is less than 0.8 mg/dl and the normal range for IgE is less than 100 IU/ml. ESR was measured using a modified version of the Westergren method (Dispette 2; Ulster Medical Products, a division of Lukens Medical Corporation, Albuquerque, New Mexico).

Statistics

Intergroup comparisons of continuous variables were performed using Student's *t* test. Bivariate correlations were performed by Pearson or Spearman's correlation test where necessary; an a priori designation system was adopted of $R < 0.40$, weakly correlated; $R = 0.40-0.69$, moderately correlated; and $R \geq 0.70$, strongly correlated. Linear regression analysis was performed for multivariate analysis. All data were analyzed using Statistical Package for the Social Sciences (SPSS) (version 13.0) for Windows (SPSS) with differences at $p < 0.05$ interpreted as statistically significant. Data were presented as mean $3 \pm \text{SEM}$.

Results

Plasma IgE levels were elevated above the normal range in 23 out of 52 Behçet's patients (44%) compared to being elevated in none of the 51 controls; $p < 0.001$. Versus controls, mean plasma IgE level was significantly higher

in the Behçet's patients (265.49 ± 42.5 vs 47.08 ± 6.6 ; $p < 0.001$). Among untreated and previously treated patients, IgE levels were significantly higher than controls ($p < 0.001$ for all comparisons). Plasma IgE levels were not statistically correlated with ESR ($r = 0.272$; $p = 0.57$), age ($r = 0.274$; $p = 0.59$), or CRP ($r = -0.48$; $p = 0.757$). ESR was moderately correlated with CRP ($r = 0.580$; $p < 0.01$). When we analyzed the patients having high IgE titers separately (23 out of 52), we obtained similar results. In this group, IgE again was not statistically correlated with ESR ($r = 0.195$; $p = 0.452$) or CRP ($r = 0.029$; $p = 0.908$), but ESR and CRP remained moderately correlated ($r = 0.649$; $p = 0.006$). Only in two patients were elevated levels of IgA detected, and in one patient an elevated IgM level was detected. Four active patients had mildly elevated leukocyte counts, and one had a mildly elevated thrombocyte count, both of which were considered to be a reflection of disease activity. When ESR, CRP, and age were included in multivariate regression analysis, the relationship still was nonsignificant, with $R^2 = 0.187$ and $p = 0.057$. In the previously untreated group, 10 out of 21 patients (47%) had high IgE levels. After the treatment was given, IgE levels increased in 6 of 10, while IgE levels decreased in 4 of 10. However, in all 10, plasma IgE levels remained higher than the upper limits of normal.

Discussions

In only a few studies have plasma IgE levels been investigated in patients with BD. However, the results of these studies were contradictory [3, 4]. In our study, we found that mean plasma IgE level was significantly higher than in controls but still only elevated above normal limits in roughly half (44%) of the patients. The clinically important point is not the statistically significant difference between the means of Behçet's patients and controls, but that 23 of 52 patients had levels higher than normal vs 0 of 51 controls. When we analyzed the two patient groups individually, the previously treated and untreated (newly diagnosed) patients, we found similar results. In both patient groups, IgE levels were higher than in controls; but, again, what is important is that approximately half of the patients in each group, 13 of 31 treated patients (41%) and 10 of 21 previously untreated patients (47%), had elevated plasma IgE. In the 10 previously untreated patients with high plasma IgE levels, IgE levels remained above normal after treatment, going down in 4 and up in 6. In the remaining, previously untreated patients' (11 out of 21) IgE levels remained in the normal range after treatment. Because of the inadequate sample size, it was not reasonable to analyze the correlation between IgE levels and acute phase reactants amid the 10 of the 21 previously untreated patients who subsequently received treatment while under observation. However, we can say that IgE levels seemed to be unrelated to treatment because, despite treatment, in 6 of 10 patients, IgE levels increased.

Among the 52 Behçet's patients, we analyzed whether there was a correlation between IgE levels and the variables

of CRP, ESR, and age. When we analyzed all patients together, including those with high IgE levels and those with normal IgE levels, we did not identify any statistically significant correlations. When we analyzed the patients having high IgE levels only, we again observed no statistically significant linear correlations between IgE and the acute phase reactants. Consequently, IgE levels did not exhibit a relationship with acute phase reactants. Supporting this result, as mentioned in the previous paragraph, treatment did not appear to have effect on IgE levels despite reducing the acute phase response.

Other results demonstrated that 18 of 52 (35%) patients had a positive pathergy test and 19 of 52 (37%) had a positive HLA-B51. Among the 18 pathergy-positive patients, 6 had high IgE, and among the 19 HLA-B51-positive patients, 7 had high IgE levels. We did not include these variables in correlation and logistic regression analyses because of inadequate sample sizes. Therefore, we cannot identify their relationship with IgE levels with any level of certainty; however, it does not appear that there is any significant correlation between these variables, given the results we observed.

The pathogenesis of BD is still unknown. Many hypotheses have been offered; however the etiology seems to be multifactorial, and the participating components are not clear [5, 6]. There is no clear evidence to discern if IgE

plays a role in the pathogenesis of the disease or if elevated levels are secondary to the disease.

In conclusion, (1) we have identified that a significant percentage (40–50%) of patients with both treated and untreated BD have above-normal plasma levels of IgE; however, confirmative studies are required from different countries; (2) IgE levels appear to be independent of disease activity and treatment response; and (3) although the sensitivity and specificity of elevated plasma IgE for Behçet's are low, such an elevated level, especially in a patient with aphthous ulcers, warrants consideration of BD.

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