Cytomegalovirus Antibody Titers in Patients with Behcet’s Disease

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Purpose: We aimed to measure the titers of Immunoglobulin G (IgG) formed against latent microbial agents, such as Cytomegalovirus (CMV), in patients with Behcet's disease (BD) and to compare with healthy population.

Method: Forty-four patients with BD who were or were not receiving immunosuppressive treatment who had their CMV immunoglobulin G (IgG) titers measured and a sixty nine healthy people (control groups) were retrospectively examined. CMV IgG titers in the patients with Behcet's disease and control groups were compared. Values above the cut-off (cut-off for CMV IgG: 6.00 IU/mL) were regarded as positive.

Findings: At the time of the tests, 18.2% of patients were not receiving any treatment, 40.9% were receiving Colchicum treatment, and 40.9% were receiving immunosuppressive treatment. CMV IgG values were positive in all of our patients and CMV IgG titers were significantly lower in the patient group than in the control group (p=0.012).

Conclusion: CMV may cause serious recurrent infections, particularly in patients who undergo immunosuppressive treatment. In the case of Behcet's disease, determining the initial titration values of CMV infection prior to immunosuppressive treatment may provide an early diagnosis and treatment for recurrent CMV infection.

Keywords: Behcet's disease; Cytomegalovirus; Immunosuppressive treatment

Introduction

Behcet's Disease (BD), typically affects young adults and is more common in men. Its aetiology is unknown. Genetic, infectious and immune mechanisms may play a role [1]. Similar to other autoimmune diseases, in people with genetic predisposition, BD may occur with abnormal activity triggered by bacterial and viral agents and some chemicals and heavy metals [2].

Among environmental agents, few viral agents may play a part, including Herpes Simplex Virus (HSV)-1 and Cytomegalovirus (CMV) [3,4].

During the course of BD [5] and in some of its clinical manifestations such as recurrent oral ulcers, CMV has been considered to be a potential cause [6]; the latent virus has been shown to cause some complications due to immunosuppressive agents used in the treatment of BD [7]. Patients with autoimmune diseases are particularly susceptible to CMV infection due to an impaired immune system and frequent immunosuppressive treatments [8]. HSV DNA levels and serum antibody levels against the virus are higher in patients with BD than in control patients [4]. Only a few studies have investigated the relationship between CMV infection and survival in patients with autoimmune disorders [8].

Where there is no possibility of CMV PCR or viral culture, CMV infection may be followed up according to changes in antibody titer. We looked at CMV IgG titers in the absence of activation of Behcet's patients who were followed up in our outpatient clinic. In our study, we also compared the incidence rates of CMV infection in patients with Behcet’s disease and the normal population of serum antibodies in the affected patients.

Materials and Methods

Forty-four patients with BD (patient group) who had routine check-ups between 1 June 2015 and 1 September 2017 at the Internal Diseases polyclinic who were or were not receiving immunosuppressive treatment and who had their CMV immunoglobulin G (IgG) titers measured and a 69 healthy people (control group) were included; they were retrospectively examined. Blood samples of subjects in both groups were collected via venipuncture performing by a trained staff member; subsequently, the samples were centrifuged for 10 min at 5000 rpm. Serum samples separated from blood were stored in a cooler at -20°C. Hyperlipaemic, haemolysed or contaminated samples were not included in the evaluation. Samples including particles were centrifuged at centrifugation. Following the completion of serum collection, the samples were taken out of the cooler and brought to room temperature. The samples were analyzed by Enzyme-Linked Immunosorbent Assay (ELISA) using appropriate kits (CMV IgG; Abbott, USA) and an appropriate device (Architect i200 SR; Abbott, USA) in accordance with the manufacturer's instructions. Values above the cut-off (cut-off for CMV IgG: 6.00 IU/mL) were deemed as positive. Patients with a systemic or an additional rheumatologic
disease besides BD were not included. Approval from the Ethics Committee of the university was obtained.

Statistical Methods

Descriptive statistical analysis was used; mean and standard deviation were used for normally distributed numerical variables, and median and minimum-maximum were used for non-normally distributed numerical variables. The Kolmogorov-Smirnov test was used for tests of normality. The t-test, Mann-Whitney U test and chi-square test were used for evaluating differences between the patient and control groups. A p-value of <0.05 was considered to be statistically significant. The SPSS 21.0 package programme (Version 21.0; Microsoft Co., Chicago, IL, USA) was used for evaluating data.

Results

The patient group comprised 27 men (61.4%) and 17 women (38.6%). The mean age of the patients was 38 ± 10.37 years. At the time of the tests, 18.2% of patients were not receiving any treatment, 40.9% were receiving Colchicum treatment, and 40.9% were receiving immunosuppressive (azathioprine, methotrexate and corticosteroid) treatment (Table 1). Duration of illness ranged from minimum 1 to maximum 30 years (Median: 4 years) (Figure 1).

![Figure 1: Duration of illness.](image)

Table 1: General information about patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Group</td>
<td>CMV IgG (IU/mL)</td>
<td>54</td>
<td>250</td>
</tr>
<tr>
<td>Control Group</td>
<td>CMV IgG (IU/mL)</td>
<td>54</td>
<td>250</td>
</tr>
</tbody>
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Table 2: Titration values of patient and control group.

Discussion

The role of viral agents in the pathogenesis of inflammatory rheumatic diseases is a matter of debate. In people with genetic predisposition, exogenous triggers including bacterial and viral (such as HSV and CMV) infections result in phenotypic expression of the disease by causing an irregularity in the immune system.

In a study conducted in Turkey, HSV-1, HSV-2, EBV, CMV, HHV-6 and parvovirus B19 were investigated to determine the aetiology of ankylosing Spondylitis and BD; the possibility of these viral agents having a role was not supported [9]. We looked at rates of encountering CMV in our patients and found that antibody titer was positive in all of our patients.

CMV may cause lifelong latent infections in ≥ 70% of the population [10,11] and get activated with deterioration of the host immune system [12]. People with autoimmune diseases are particularly susceptible to CMV infection due to an impaired immune system and frequent immunosuppressive treatment. The virus can be transmitted to endothelium cells or fibroblasts and may negatively affect the prognosis of patients with immune deficiency [13]. In our study, at the time of the tests 40.9% of patients were receiving immunosuppressive (azathioprine, methotrexate and corticosteroid) treatment.

Sari et al. reported that CMV colitis developed in patients who were monitored due to the presence of neuro-BD and who were treated with tumor necrosis factor alpha inhibitor [14]. In case studies on patients with BD with intestinal involvement, there was CMV involvement in intestinal lesions in patients undergoing immunosuppressive treatment; that lesions regressed when immunosuppressive treatment was stopped and antiviral treatment was initiated [15,16]. Studies showing that the development of local immunosuppression as a result of intravitreal fluocinolone acetonide implant (Retisert) performed on patients with recurrent Behcet’s uveitis increased CMV retinitis or endotheliitis risk also support the abovementioned studies [17,18]. In the present study, we did not observe any infection related to CMV in the patient group although a significant proportion of patients receive immunosuppressive therapy. We can explain this with no activation of any of our patients.

In their study regarding the role of CMV in recurrent aphthous ulcers in patients with BD, Lee et al. reported that they found the CMV IgG response to be significantly lower in the patient group than in the control group [6]. Similarly, Seoudi et al. detected lower levels of CMV IgG in the patient group (with BD) than in the control group [19]. Seoudi mentioned that the detection of low levels of CMV IgG was...
associated with a defect in the function of toll-like receptors 1/2, which operate as the first receptor in the detection of CMV [20]. Similar to these studies, in our study, CMV IgG titers in patients with BD was significantly lower in the patient group than in the control group. Lower antibody titers against CMV in patients with BD may suggest that CMV-associated infection may increase. Since CMV IgG titrations before patients receive immunosuppressive therapy are unknown, there is a need for controlled studies to fully understand the effect of the treatment on it.

Conclusion

While many factors including primary infectious factors are considered to be the cause of autoimmune diseases, there is no consensus on the cause. However, infectious agents that may remain latent for a long period may result in serious recurrent infections, particularly in patients who receive immunosuppressive treatment; this may result in a delay in diagnosis. One of these, CMV, may remain latent and become particularly active under immunosuppressive therapy. An infection such as hepatitis B, which is at risk of activation, can be followed by HBV DNA, but where there is no possibility of PCR and viral culture for CMV, the activity of the CMV disease can be evaluated according to the changes in the CMV IgG titration values of the patients. For this, antibody titers should be assessed during inactive periods of patients and these values should be compared with titration values measured at any activation. As a result of this comparison, we believe that there will be a positive contribution to mortality and morbidity since it will allow the early start of treatment when changes are made in a shorter time.

References