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Review Article

The Value of Esr, Crp, and the Iran Behcet's Disease Dynamic Activity Measure (Ibddam) in Differentiating the Active or Inactive Phases for the Manifestations of Behcet's Disease

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Abstract

There is a correlation of ESR, CRP, and BDCAF (one of the Disease Activity Measures of Behcet's Disease), as shown by Melikoglu and TopKarci in Turkish patients. The aim of this study is to look for the value of them in Iranian patients, but with the IBDDAM instead of BDCAF.

Materials and Methods

Patients (135) were selected as consecutive patients, seen at the Behcet's Unit of the Rheumatology Research Center, Tehran University of Medical Sciences (TUMS), Tehran, Iran. ESR, CRP, and IBDDAM were checked in patients having an active manifestation of the BD and compared with other patients having that symptom in the past but not at the day of examination.

Results

Active Oral aphthosis (OA), genital aphthosis (GA), anterior uveitis (AU), and retinal vasculitis (RV) were related to high values of CRP with p values of 0.03, 0.009, <0.0001, and 0.05. Active GA, AU, posterior uveitis (PU), RV, vascular manifestations (VM), and Joint manifestations (JM), were related to high values of ESR with p values of 0.02, <0.0001, <0.0001, <0.0001, 0.05, and 0.001. Active GA, eye involvement (EI), AU, and PU, were related with abnormal IBDDAM values, with p values of 0.001, <0.0001, <0.0001, and <0.0001.

Conclusion

ESR and/or CRP were significantly higher in active cases of OA, GA, AU, PU, RV, VM, JM, and NM. IBDDAM was higher in OA, GA, EI, AU, PU, and RV.

Keywords: Behcet's Disease; Esr; Crp; Iran Behcet's Disease Dynamic Activity Measure; Ibddam, Behcet's Disease Activity Measure

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Abbrevations

BD: Behcet's Disease

IBDDAM: Iranian Behçet's disease Dynamic Measure

BDCAF: Behcet's Disease Current Activity Form

ICBD: International Criteria for Behcet's Disease

OA: Oral aphthosis

GA: Genital aphthosis

PF: Pseudofolliculitis

EN: Erythema nodosum

PT: Pathergy test

EI: Eye Involvement

AU: Anterior uveitis

PU: Posterior uveitis

RV: Retinal vasculitis

VM: Vascular manifestations

JM: Joint Manifestation

NM: Neurological Manifestations

Introduction

Behcet's Disease (BD) is a multisystem disease, classified as vasculitides by the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, in the Variable Vessel Vasculitis subgroup [1]. However, some authors, still classify the disease among the autoinflammatory diseases [2]. BD progresses by relapsing attacks and remissions. In each attack, one to several organs may be involved. After each attack, a recovery period starts until a remission occurs. The duration of the recovery period differs from one attack to another, and for different organs. The remission may be complete, with a return to normal of the involved organ (restitution ad integrum), or followed by some sequels. This particular characteristic of BD (recurrent attack and remissions, with different durations) differentiates BD from other vasculitides [3].

Although the disease was known since the antiquity, by Hippocrates [4], other cases of the disease were also presented before Behcet, especially by Shigeta [5] and by Adamanthiades [6]. However, it was Hulusi Behcet, a Turkish Dermatologist that described it, in 1937, as a separate disease [7]. He presented it as a triple complex disease, in 3 patients, involving the mucous membrane of mouth and genitalia (oral aphthosis, genital aphthosis), and the involvement of the eye (anterior uveitis with hypopyon). Later on, other manifestations of the disease started to be described, mainly the skin, vascular, and neurologic manifestations[3, 8]. There is no laboratory data characteristic of BD, but few lab data may reflect the activity of clinical signs and symptoms, which are the ESR and CRP. Apart these lab tests, there are Behcet's Disease Activity Indexes, which calculate the activity of the disease and may show the state of the disease [9-12]. As said before, the disease progress by attacks and remissions. The remission may be spontaneous or produced by the treatment and it is essential to find it.

As said before, the duration of each attack and the outcome of the attack (Restitutio ad Integrum, or recovery with some sequels) is different for each organ, but also from one attack to another for the same organ. ESR, CRP, and calculation of a disease activity index may be of help to try to foresee the outcome. In all these scoring systems, the calculation of the disease activity is based on clinical features only [13]. The IBDDAM (Iranian Behcet's Disease Dynamic Activity Measure) was designed as a good tool for the disease activity calculation [11] and differs from the BDCAF (Behcet's Disease Current Activity Form) [13]. Laboratory data, especially the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as an acute phase reactant is used in routine clinical practice, however, their relation with a BD disease activity is a big question. Melikoglu and Topkarci have looked for it in Turkish patients [14]. The aim of this study is to look in Iranian patients if their abnormal values are seen more frequently in the presence of active manifestations of the disease. We used IBDDAM instead

of BDCAF used by Melikoglu and Topkarci. We wanted to evaluate if a high value of ESR, CRP, and IBDDAM were seen more in major manifestations of BD in their active phase.

Materials and Methods

135 consecutive patients with BD who fulfilled the ICBD criteria (International Criteria for Behcet's Disease) were selected [15]. Patients with anemia, infections, malignant disorders, renal disease, hepatic disease, pregnancy, and associated with other collagen vascular disease, were excluded from the study.

1- Clinical assessments

For all of the patients, demographic information including age, sex, disease duration, were written. Then for each patient IBDDAM was calculated and written in the questionnaire page. On the day of evaluation, for each organ involvement, patients were divided into two groups of active or inactive symptoms for that organ. ESR, CRP, and IBDDAM were calculated for that organ for comparison between the active and the inactive group.

2- IBDDAM calculation

The following pointing system was used for IBDDAM calculation.

- Oral aphthosis: one point for each five aphthous lesions.
- Genital aphthosis: one point for each lesion.
- Skin lesions: pseudofolliculitis 1 point for every ten lesions, erythema nodosum 1 point for every five lesions.
- Ocular lesions: anterior uveitis, 1 to 4 points are given for flare, hypopyon, cells, and keratic precipitate. Posterior uveitis: 1–4 points are given for cell, snowball, and snow banking. The total is multiplied by 2 (severity index). Retinal vasculitis: 1–4 points are given for disc edema, macular edema, retinal edema, periphlebitis, periarteritis, and papillitis. The total is multiplied by 3 (severity index). Visual acuity by Snellen chart, is first adjusted to the 10th scale (10/10 normal vision), and then the observed number is subtracted from 10 and the remainder is multiplied by 2 (severity index). For example, a visual acuity of 6/10 would give $(10 - 6) \times 2 = 8$. The calculation is made separately for each eye.
- Joints: one point for arthralgia regardless of the number of involved joints, 2 points for monoarthritis, and 3 points for polyarthritis.
- Central nervous system (CNS) involvement: one point for headache, 3 points for mild, and 6 points for moderate to severe CNS involvement.
- Vascular involvement: 1 point for superficial phlebitis, 2 points for deep vein thrombosis (each vein), and 6 points for each large vessel involvement.
- Gastrointestinal tract: 3 points for mild and 6 points for moderate to severe manifestations (chronic diarrhea, rectal bleeding, and abdominal pain).
- Epididymitis: 2 points.
- Positive pathergy test: 1 point.
- Duration of lesions: if a lesion does not heal in 1 month the same points are given for each additional month of activity [11,12].

3- Laboratory assessments

Erythrocyte sedimentation rate (ESR) was measured by the Westergren method. CRP concentration was evaluated by nephelometry. As the results were given by different methods of analysis with different normal ranges, the results were adjusted to the normal range below 6 mg per liter.

4- Statistical analysis

All statistical analysis was performed using the SPSS software package program. The number of cases (active and inactive), the mean, and the standard deviation (SD) is given. The t-test was used for the comparison. In case of non-parametric distribution, Kruskal-Wallis test was used. If Kruskal-Wallis test was used,

the result was specified by an asterisk (*) over the p value.

Results

135 patients were selected as consecutive patients seen at the Behcet's Unit of the Rheumatology Research Center, Tehran University of Medical Sciences.

ESR, CRP and IBDDAM were calculated for each patient. Then the patient was evaluated for the symptoms he/she ever had (from the start of the disease until today). For each symptom, the patient was classified as having an active symptom on the day of the evaluation or being inactive for that symptom.

There were 80 males and 55 females, with an age range of 16 to 65 years. The mean age (the day of the evaluation) was 37.25 years with a standard deviation (SD) of 10.96 (Table 1).

The complete results of ESR, CRP, and IBDDAM for different organ involvement in active state and in an inactive state (in remission), and their comparison are given in Table 2.

- Oral Aphthosis (OA): The number of active cases was 59 patients. The mean ESR was 24.25 mm in the first hour (SD 22.4), the mean CRP was 13.3 (SD 19), and the mean IBDDAM was 13.3 (SD 15.5). For inactive cases the number was 76, mean ESR 18.1 (SD 20.3), mean CRP 8.4 (SD 6.9), and mean IBDDAM 21 (SD 27). The p value of the difference between active and inactive cases was 0.06 for ESR, 0.03* for CRP, and 0.5 for IBDDAM.

- Genital Aphthosis (GA): The number of active cases was 14 patients. The mean ESR was 34.1 mm in the first hour (SD 21.6), the mean CRP was 19.2 (SD 18.0), and the mean IBDDAM was 6.5 (SD 9.4). For inactive cases the number was 73, mean ESR 20.5 (SD 10.5), mean CRP 17.5 (SD 15.4), and mean IBDDAM 15.4 (SD 22.2). The p value of the difference between active and inactive cases was 0.02* for ESR, 0.009* for CRP, and 0.001* for IBDDAM.

- Skin (SK): The number of active cases was 12 patients. The mean ESR was 30.7 mm in the first hour (SD 25.4), the mean CRP was 19.2 (SD 25.1), and the mean IBDDAM was 14.7 (SD 35.4). For inactive cases the number was 23, mean ESR 19.9 (SD 16.5), mean CRP 9.8 (SD 11.5), and mean IBDDAM 11.6 (SD 13.9). The p value of the difference between active and inactive cases was 0.33 for ESR, 0.46 for CRP, and 0.38 for IBDDAM.

- Pseudofolliculitis (PF): The number of active cases was 6 patients. The mean ESR was 25.8 (SD 21.0), the mean CRP was 15.3 (SD 25.1), and the mean IBDDAM was 26.0 (SD 49.4). For inactive cases the number was 29, mean ESR 23.1 (SD 20.5), mean CRP 12.6 (SD 16.2), and mean IBDDAM 9.9 (SD 12.8). The p value of the difference between active and inactive cases was 0.36 for ESR, 0.25 for CRP, and 0.22 for IBDDAM.

- Erythema nodosum (EN): The number of active cases was 8 patients. The mean ESR was 37.0 mm at the first hour (SD 25.9), the mean CRP was 27.1 (SD 27.8), and the mean IBDDAM was 3.4 (SD 1.8). For inactive cases the number was 27, mean ESR 19.7 (SD 17.0), mean CRP 8.9 (SD 10.8), and mean IBDDAM 15.4 (SD 25.7). The p value of the difference between active and inactive cases was 0.13 for ESR, 0.12 for CRP, and 0.10* for IBDDAM.

- Pathergy test (PT): The number of active cases was 19 patients. The mean ESR was 20.95 (SD 14.7), the mean CRP was 15.8 (SD 23.6), and the mean IBDDAM was 20.6 (SD 29.4). For inactive cases the number was 49, mean ESR 25.6 (SD 27.1), mean CRP 11.6 (SD 19.2), and mean IBDDAM 13.7 (SD 17.5). The p value of the difference between active and inactive cases was 0.2 for ESR, 0.09 for CRP, and 0.07 for IBDDAM .

- Eye Involvement (EI): The number of active cases was 68 patients. The mean ESR was 11.9 (SD 9.9), the mean CRP was 6.7 (SD 13.6), and the mean IBDDAM was 31.7 (SD 24.1). For inactive cases the number was 24, mean ESR 20.9 (SD 25.4), mean CRP 12.6 (SD 20.1), and mean IBDDAM 4.4 (SD 6.7). The p value of the difference between active and inactive cases was 0.3 for ESR, 0.5 for CRP, and 0.000* for IBDDAM .

- Anterior uveitis (AU): The number of active cases was 16 patients. The mean ESR was 16.4 (SD 12.9), the mean CRP was 15.5 (SD 23.3), and the mean IBDDAM was 44.4 (SD 36.8). For inactive cases the number was 52, mean ESR 10.6 (SD 8.4), mean CRP 3.9(SD 7.2), and mean IBDDAM 27.8 (SD 17.5). The p value of the difference between active and inactive cases was 0.000 for ESR, 0.000 for CRP, and 0.000 for IBDDAM.

- Posterior uveitis (PU): The number of active cases was 60 patients. The mean ESR was 11.4 (SD 9.3), the mean CRP was 6.1 (SD 13.6), and the mean IBDDAM was 32.6 (SD 24.8). For inactive cases the number was 8, mean ESR 15.7 (SD 13.6), mean CRP 10.5 (SD 14.4), and mean IBDDAM 25.0 (SD 17.4). The p value of the difference between active and inactive cases was 0.000* for ESR, 0.06 for CRP, and 0.000* for IBDDAM.

- Retinal Vasculitis (RV): The number of active cases was 45 patients. The mean ESR was 10.2 (SD 8.0), the mean CRP was 6.6 (SD 15.5), and the mean IBDDAM was 38.8 (SD 25.7). For inactive cases the number was 23, mean ESR 15.3 (SD 12.2), mean CRP 6.7 (SD 9.4), and mean IBDDAM 17.8 (SD 11.8). The p value of the difference between active and inactive cases was 0.000* for ESR, 0.05 for CRP, and 0.000* for IBDDAM

- Vascular manifestations (VM): The number of active cases was 10 patients. The mean ESR was 59 (SD 28.1), the mean CRP was 38.8 (SD 20.1), and the mean IBDDAM was 5.1 (SD 3.6). For inactive cases the number was 3, mean ESR 21.3 (SD 18.3), mean CRP 10 (SD 17.3), and mean IBDDAM 3.0 (SD 2.6). The p value of the difference between active and inactive cases was 0.05* for ESR, 0.11 for CRP, and 0.29 for IBDDAM.

- Joint Manifestation (JM): The number of active cases was 17 patients. The mean ESR was 46.2 (SD 21.8), the mean CRP was 20.2 (SD 21.1), and the mean IBDDAM was 5.3 (SD 5.6). For inactive cases the number was 9, mean ESR 19.0 (SD 20.8), mean CRP 14.3 (SD 22.0), and mean IBDDAM 5.9 (SD 7.9). The p value of the difference between active and inactive cases was 0.001* for ESR, 0.43 for CRP, and 0.56 for IBDDAM

- Neurological Manifestations (NM): The number of active cases was 2 patients. The mean ESR was 18.0 (SD 4.2), the mean CRP was 2.0 (SD 2.8), and the mean IBDDAM was 6.5 (SD 0.7). For inactive cases the number was 1, mean ESR 7, mean CRP 3, and mean IBDDAM 42. The p value of the difference between active and inactive cases was 1 for ESR, 1 for CRP, and 1 for IBDDAM

In summary, 135 patients had BD. The active lesion of oral aphthosis was related to the elevation of CRP (P value: 0.03), which is statistically significant. Genital aphthosis was also related to the ESR and IBDDAM elevation (P=0.02 and P=0.01 respectively). Activation of Skin lesions, pathergy test, and CNS involvement were not related to ESR, CRP and IBDDAM elevation. Anterior uveitis had a strong relation with ESR, CRP and IBDDAM (P=0.000, P=0.000 and P=0.000, respectively). Posterior uveitis and retinal vasculitis, had the same results and were related with ESR and IBDDAM (P=0.000 and P=0.000 respectively). They were not related to CRP. Vascular and joint manifestations were related to the ESR, especially articular involvement (P=0.05 and P=0.001 respectively).

Discussion

As said before, BD is characterized by repeated episodes of attacks and remissions. The clinical picture may vary from one attack to another. As an example, pseudofolliculitis may be the presentation of skin involvement in one attack, but erythema nodosum in another. The severity of each attack may differ. The extent of organ involvement may also differ during different attacks (one or several organs may be involved together). Moreover, the duration of remissions may also vary between attacks. All these variables make the evaluation of the disease activity in BD very difficult. The main difficulty is to discover whether the recovery of the disease is due to the natural course of the disease or to the treatment [11].

IBDDAM is a reliable tool for the evaluation of the disease, if the patient reports his/her symptoms correctly. IBDDAM is a valuable tool for research purposes, giving a quoted activity index for Behcet's disease, making statistical calculation easy. It is a very useful management tool in the hand of a physician with little experience in managing Behcet's

disease. This tool can be used for disease activity and disease severity. Other tools for the evaluation of BD activity were, the BDCAF, which was developed by Chamberlain, the European scheme initially developed in the UK [16].

It was important to find if ESR and CRP were related to the attacks of BD. In 2014, Melikoglu showed that high CRP is related to a newly developed erythema nodosum, superficial thrombophlebitis, joint involvement, and BDCAF [14]. In Iran, ESR was elevated in only 46.5% of patients. It was between 21 and 50 mm (at the first hour) in 32.6% of patients, between 51 and 100 mm in 13.8%, and superior to 100 in 1.3% of patients. These were mainly patients with active disease, entering the registry for the first time [17]. In Iran, elevated ESR was seen more in patients with genital ulcers (p=0.049).

Our study was designed for the evaluation of ESR and CRP, as acute phase reactants, and their relation with the disease activity and IBDDAM.

Multiple inflammatory mediators have been searched in patients with BD, and in some of these studies, it has been shown that some of these mediators were related to the disease activity, as said before by Melikoglu et al. In 1996 Ozoran et al studied the mean ESR, CRP, C3 and C4 levels of active BD patients. They were found to be significantly higher than those of the inactive BD patient group [18]. In 2004, Adam and colleagues showed that serum CRP and IL-6 values were significantly higher in active disease than in the healthy controls ($P<0.05$), but there was no significant difference in the levels of Serum procalcitonin (PCT) in the two group [19]. Karadağ and colleagues, in 2006, have compared the serum levels of IL-6, IL-8, TNF-α, C reactive protein and the heat shock protein 70 in patients with active or inactive Behcet's Disease. They showed that patients with active disease, had significantly higher mean serum levels of IL-6, IL-8, TNF-α, and CRP compared to patients with inactive disease or the controls (overall, $P<0.05$). The HSP 70 levels did not differ significantly between patients with active disease and patients with inactive disease, but was significantly higher in BD patients than in controls [20]. Katsantonis and colleagues showed the reliability of IL-8 as a serological marker for the assessment of the disease activity at any time of the disease progression [21]. Onat and colleagues, in 2007, showed an elevation of IgE in patients with BD. But, this elevation was not correlated with levels of acute phase reactants or disease activity [22].

Conclusion

In this study, we showed that ESR and/or CRP were significantly higher in active cases of OA, GA, AU, PU, RV, VM, JM, and NM. IBDDAM was higher in OA, GA, EI, AU, PU, and RV.

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