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ORIGINAL ARTICLE

The utility of immunoglobulin A/complement 3 and immunoglobulin G/immunoglobulin M ratios in the assessment of disease activation in patients with Behçet disease

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ABSTRACT

Objective: Pathogenesis of Behçet disease (BD) has not yet been clearly revealed and there is no ideal test for the estimation of disease activation at present. This study aimed to assess the efficiencies of IgG/IgM and IgA/C3 ratios in determining activation of BD.

Method: This retrospective cohort study consisted of 140 patients with BD. Patients were divided into two groups: (1) active BD ($n = 89$) and (2) inactive BD ($n = 51$) and were compared in terms of demographic features, clinical characteristics and laboratory test results. IgA/C3 and IgG/IgM ratios were compared according to organ system involvement; receiver operating characteristic (ROC) curve analysis was performed in order to assess the performance of IgA/C3 and IgG/IgM ratios in determining patient disease status.

Results: Significantly higher levels of erythrocyte sedimentation rate, C-reactive protein, IgA, G, C4, IgA/C3, IgG/IgM ratios ($p = .007$ for IgA and $p < .001$ for others) and significantly lower levels of IgM and C3 were observed in patients with active BD ($p < .001$). The IgG/IgM ratio was significantly higher in patients with vascular involvement ($p = .017$) and the IgA/C3 ratio was significantly higher in patients with arthritis ($p = .007$). Cut-off values of 0.019 (70.8% sensitivity, 62% specificity) and 7.08 (84.3% sensitivity, 80% specificity) were determined for IgA/C3 and IgG/IgM ratios, respectively.

Conclusion: IgA/C3 and IgG/IgM ratios may be used as additional parameters for the assessment of BD status.

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Behçet disease; immunoglobulins; complement levels; cut-off value; IgA/C3 and IgG/IgM ratios

Introduction

Behçet disease (BD) is a complex vasculitis-like syndrome that involves multiple systems [1,2]. Its prevalence varies significantly depending on geographic and racial factors [3]. Clinical manifestations range from recurrent oral aphthous ulcerations to serious organ system complications. Due to the heterogeneity in disease course and presentation in patients, it may be challenging for physicians to establish appropriate management protocols [1,3]. For this reason, comprehensive evaluation of the patients and multidisciplinary approaches are necessary in order to achieve favourable outcomes.

The main goals of BD treatment are to control the excessive inflammatory process during exacerbations and to prevent irreversible organ damage [4]. Thus, detecting and treating BD activation is crucial for treatment. However, pathogenesis of BD has not been clearly revealed and there is no ideal test for the estimation of disease activation at present [5]. Physical examination, various laboratory tests and radiologic screening modalities may be used for the assessment of disease activation with variable results but it may be still challenging for physicians to reach a conclusion [1,6–8]. Therefore, researchers have been focussed on finding alternative methods for the evaluation of disease activation [9–13].

Association between immunoglobulin (Ig) levels and activation of BD has been investigated in various studies [14–19]. The majority of these indicated that activation of BD was observed in patients with higher Ig levels, probably due to the presence of immune complexes [14–20]. However, none gave definitive results and estimation of Igs is not a routine part of evaluation for BD [14–19].

The ratios of IgG to IgM (IgG/IgM ratio) and IgA to complement 3 (IgA/C3) have begun to be used as novel prognostic indexes for predicting the prognosis of various autoimmune diseases [21–25]. However, to the best of our knowledge, no published study has evaluated the efficacy of these indexes for the assessment of disease activation in BD.

The aim of this study was to assess the efficiencies of IgG/IgM and IgA/C3 ratios in determining activation of BD.

Methods

Enrolment of patients

This retrospective cohort study consisted of 140 patients with BD who underwent follow-up at the Department of Dermatology and Venereology, Ufuk University Hospital

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between January 1, 2010 and December 31, 2019. The required data were extracted from the institutional electronic database of Ufuk University Hospital. The study protocol was approved by Ankara City Hospital Ethics Committee (reference number E1-20-699) and informed consent was obtained from all participants.

All cases with known immunoglobulin A, E, G, M (IgA, E, G, M) and complement 3, 4 (C3, C 4) levels upon admission to hospital were initially included in this study. However, patients without sufficient information regarding disease status and required laboratory tests upon admission were later excluded. Moreover, patients with known risk factors that might affect the study parameters, such as immunoglobulin/complement deficiencies or infection were also excluded. Patients were divided into two groups based on their disease status upon admission: (1) Active BD and (2) Inactive BD. Afterwards, patients were compared in terms of demographic features, clinical characteristics and laboratory test results.

Investigation of clinical and laboratory parameters

Age, gender, age at onset of disease, duration of disease, clinical manifestations (rates of oral ulceration, urogenital lesions, cutaneous lesions, ocular disease, neurologic disease, vascular disease, pulmonary disease, arthritis, gastrointestinal involvement) and laboratory parameters (erythrocyte sedimentation rate, C-reactive protein, IgA, E, G, M, C3, C4 levels, IgA/C3 and IgG/IgM ratios) upon admission to hospital were compared between the groups. Furthermore, comparisons of IgA/C3 and IgG/IgM ratios between the patients according to system involvement were performed. Lastly, a receiver operating characteristic (ROC) curve analysis was done in order to assess the performances of IgA/C3 and IgG/IgM ratios in determining patient disease status upon admission to the hospital.

Disease activity was evaluated based on criteria determined by the Behcet Disease Research Committee of Japan in 2003 (6). All patients were evaluated in terms of disease activity upon admission to hospital by expert dermatologists.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows (IBM Corp., Armonk, New York, USA). Visual (histograms, probability plots) and analytical methods (Kolmogrov–Smirnov tests) were used in order to determine the normality of distribution. As the data were not normally distributed, medians and interquartile range values were used for descriptive analysis. Additionally, a Mann–Whitney *U* test was conducted to compare median values and a Chi-square test was used to compare categorical variables among the groups. Receiver operating characteristic (ROC) curves were used to assess the performance of IgA/C3 and IgG/IgM ratios in determining the patient disease status upon admission to the hospital. Youden's index was applied to ROC curve to determine the best cut-off value [26]. A two-tailed p-value $<.05$ was regarded as statistically significant.

Results

There were 89 and 51 patients in the active and inactive BD groups, respectively. Demographic features and clinical characteristic of the patients with active and inactive Behcet disease are shown in Table 1. Median duration of BD was significantly longer in the inactive patients ($p = .005$). Moreover, ocular, neurologic disease and arthritis were significantly more common in patients with active BD (p-values = .005, .04 and .001, respectively). Significantly higher levels of erythrocyte sedimentation rate, C-reactive protein, IgA, G, C4, IgA/C3, IgG/IgM ratios ($p = .007$ for IgA and $p < .001$ for the others) and significantly lower levels of IgM and C3 were observed in patients with active BD ($p < .001$). The two groups were similar in terms of IgE levels ($p = .74$).

Comparisons of IgA/C3 and IgG/IgM ratios between the patients according to system involvement are shown in Table 2. The median IgG/IgM ratio was significantly higher in patients with vascular involvement ($p = .017$) and the median IgA/C3 ratio was significantly higher in patients with arthritis ($p = .007$).

ROC curve analysis for assessing the performance of IgA/C3 and IgG/IgM ratios in determining activation of Behcet disease is summarised in Table 3. Area under the curve (AUC) values were calculated as 0.748 (95% CI: 0.662–0.833) and 0.882 (95% CI: 0.823–0.941) for IgA/C3 and IgG/IgM ratios, respectively. The IgA/C3 and IgG/IgM ratio values in ROC curves with the best balance of sensitivity/specificity were 0.019 (70.8% sensitivity, 62% specificity) and 7.08 (84.3% sensitivity and 80% specificity), respectively, for determining the activation of Behcet disease according to the results obtained from Youden's index.

Discussion

BD is a multisystem chronic systemic inflammatory disorder characterised by episodes of remission and exacerbation [1,3]. Although the aetiology of BD is still unclear, impaired immune system activation due to various triggering factors in patients with genetic predisposition seems to be the most possible mechanism underlying this complex disease [27,28]. Previous studies have postulated that molecular mimicry, environmental triggering antigens, T-helper mediated immune response together with imbalance between pro and anti-inflammatory cytokines all contribute to the development of BD [1,5,27].

There is no curative treatment for BD at present. Thus, management strategies mainly focus on controlling the excessive immune-mediated process during the exacerbations [4]. If active BD can be detected at earlier stages and appropriate regimens can be started, physicians might better prevent irreversible organ system damage [1,4,5]. However, evaluation of disease activation is challenging in some situations and additional laboratory tests may be necessary to make a more definitive diagnosis. For this reason,

Table 1. Demographic features and clinical characteristic of the patients with active and inactive Behcet disease.

Variables	Active BD ($n = 89$)	Inactive BD ($n = 51$)	p-Values
Age (years)(median, IQR)[a]	30 (18)	37 (23)	.08
Gender [n (%)][b]			
Male	45 (50.6%)	21(41.2%)	.28
Female	44 (49.4%)	30 (58.8%)	
Age at onset of disease (years)(median, IQR)[a]	25 (12.50)	27 (13)	.87
Duration of disease(month)(median, IQR)[a]	60 (96)	96 (180)	**.005**
Clinical manifestion [n (%)][b]			
Oral ulceration	30 (100%)	51 (100%)	1.00
Urogenital lesions	65 (73%)	32 (62.7%)	.21
Cutaneous lesions	89 (100%)	51 (100%)	1.00
Ocular disease	48 (53.9%)	15 (29.4%)	**.005**
Neurologic disease	6 (6.7%)	0 (0%)	**.04**
Vascular disease	14 (15.7%)	4 (7.8%)	.18
Pulmonary disease	4 (4.5%)	0 (0%)	.12
Arthritis	30 (33.7%)	4 (7.8%)	**.001**
Gastrointestinal involvement	4 (4.5%)	0 (0%)	.30
Laboratory parameters (median, IQR)[a]			
ESR(mm/h)	28 (17)	11 (6.5)	**<.001**
CRP (mg/dl)	9.16 (8.9)	1.70 (2.45)	**<.001**
IgA (g/L)	2.64 (1.16)	2.16 (1.67)	**.007**
IgE (UI/ml)	25 (32.7)	25 (36.5)	.74
IgM (g/L)	1.17 (0.55)	1.67 (0.8)	**<.001**
IgG (g/L)	13.5 (3.7)	9.7 (2.5)	**<.001**
C3 (mg/dl)	112.16 (27.7)	138.4 (37.5)	**<.001**
C4 (mg/dl)	31.37 (12.95)	26.82 (10.7)	**<.001**
IgA/C3 ratio	0.023 (0.01)	0.016 (0.01)	**<.001**
IgG/IgM ratio	11.45 (6.3)	5.72 (2.5)	**<.001**

BD: Behcet disease; C: complement; CRP: C-reactive protein; ESR: erytrocyte sedimentation rate; Ig: immunoglobulin; IQR: interquartile range.
Statistically significant p values ($p < 0.005$) were highlighted in bold.
[a]Statistical analysis was performed by Mann–Whitney U test.
[b]Statistical analysis was performed by Chi-square test.

Table 2. Comparison of IgA/C3 and IgG/IgM ratios between the patients according to system involvement.

Clinical manifestation	IgA/C3 ratio (median, IQR)		p-Values	IgG/IgM ratio (median, IQR)		p-Values
Urogenital lesions	+ ($n = 97$)	− ($n = 43$)	.38	+ ($n = 97$)	− ($n = 43$)	.98
	0.020 (0.01)	0.021 (0.01)		8.72 (6.9)	8.79 (8.2)	
Ocular disease	+ ($n = 63$)	− ($n = 76$)	.60	+ ($n = 63$)	− ($n = 76$)	.12
	0.021 (0.01)	0.020 (0.01)		9.24 (6.5)	7.60 (7.9)	
Neurologic disease	+ ($n = 6$)	− ($n = 134$)	.12	+ ($n = 6$)	− ($n = 134$)	.32
	0.013 (0.02)	0.021 (0.01)		11.22 (6.9)	8.76 (7.2)	
Vascular disease	+ ($n = 18$)	− ($n = 122$)	.57	+ ($n = 18$)	− ($n = 122$)	**.017**
	0.024 (0.01)	0.020 (0.01)		12.55 (4.73)	8.32 (6.58)	
Pulmonary disease	+ ($n = 4$)	− ($n = 136$)	.74	+ ($n = 4$)	− ($n = 136$)	.30
	0.019 (0.02)	0.020 (0.01)		11.09 (14.8)	8.76 (7.4)	
Arthritis	+ ($n = 34$)	− ($n = 106$)	**.007**	+ ($n = 34$)	− ($n = 106$)	.65
	0.023 (0.01)	0.019 (0.01)		9 (7.1)	8.76 (7.5)	
Gastrointestinal involvement	+ ($n = 4$)	− ($n = 136$)	.80	+ ($n = 4$)	− ($n = 136$)	.45
	0.022 (0.01)	0.020 (0.01)		6.29 (5.3)	8.77 (7.4)	

C: complement; Ig: immunoglobulin; IQR: inter-quartile range.
Statistically significant p values ($p < 0.005$) were highlighted in bold.

Table 3. ROC curve analysis for assessing the performances of IgA/C3 and IgG/IgM ratios in predicting activation of Behcet disease.

	Cut-off value for IgA/C3 ratio	Sensitivity	Specificity	p-Value
Active BD (AUC: 0.748 95% CI: 0.662–0.833)	0.019	70.8%	62%	<.001
Active BD (AUC: 0.882 95% CI: 0.823–0.941)	7.08	84.3%	80%	<.001

AUC: area under the curve; BD: Behcet disease; C3: complement 3; CI: confidence interval; IgG-M: immunoglobulin G and M; ROC: receiver operating characteristic.

researchers have been working on Supplementary methods for the evaluation of disease activation [9–12].

Association between Ig levels and BD activation has been investigated in various studies [14–19]. Bardak et al. reported higher levels of IgA, IgM, C3, and C4 levels in BD patients with active uveitis and without any other manifestation of the disease compared to a control group. Furthermore, levels of the mentioned mediators were lower in the same BD patients when they were in a convalescence period [14]. Sharief et al. demonstrated higher levels of oligoclonal IgA and M bands in cerebrospinal fluid samples of patients with active neuro-BD compared to the control group [15]. Onat et al. found increased levels of IgE in BD patients regardless of disease status [16]. Scully et al.

compared BD and recurrent aphthous stomatitis patients to healthy controls in terms of IgA, D, E, and M levels; they found significantly higher levels of IgA in patients with BD and significantly higher levels of IgD and IgE in patients with recurrent aphthous stomatitis compared to healthy controls [17]. Bireller et al. showed that IgG purified from the neuro-BD patients was associated with increased cell death and apoptosis in cultured neuroblastoma cells [18]. Lucherini et al. reported higher levels of IgD in patients with BD compared to healthy controls [19]. In the present study, significantly higher levels of IgA, G, C4 were observed in patients with active BD. These findings are consistent with previous studies [14–19]. On the other hand, IgM and C3 levels were significantly higher in patients with inactive BD and no difference was found between the groups in terms of IgE. These latter results differ from those present in the literature.

IgG/IgM and IgA/C3 ratios were used for the assessment of prognosis in various autoimmune diseases with promising results [21–25]. However, to the best of our knowledge, there are no published studies on the efficacy of the mentioned ratios for patients with BD; the present study is therefore valuable in terms of its novelty. IgA/C3 and IgG/IgM ratios were significantly higher in patients with active BD, the IgG/IgM ratio was significantly higher in patients with vascular involvement, and the IgA/C3 ratio was significantly higher in patients with arthritis. Moreover, we identified optimal cut-off values for these ratios with acceptable sensitivity and specificities. Thus, although this study included a limited number of patients, our findings may be useful for physicians in the assessment of active BD.

The main strengths of this study were its novelty, relatively higher number of study parameters and management of cases with the same physicians. However, the retrospective design and relatively low number of cases were limitations. For this reason, future prospective studies on larger populations are necessary to confirm these results.

In conclusion, IgA/C3 and IgG/IgM ratios may be used as additional parameters for the assessment of BD status.

Author contributions

Didem Dincer participated in study design and manuscript writing. Efsun Tanacan participated in study design, data collection, statistical analysis and manuscript writing. F. Gulru Erdogan participated in study design, manuscript writing and critically reviewing the manuscript. Aysel Gurler participated in supervision and manuscript writing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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