ORIGINAL ARTICLE

JIACM 2019; 20(3-4): 190-94

Fatigue in Rheumatoid Arthritis as Measured by BRAF-MDQ Score and its Relation to Serum Interleukin-6 Level

RS Taneja, Yogita Sharma***

Abstract

Background: Fatigue, as a symptom, in patients with RA is not very commonly assessed by clinicians. At different times pain, stress, depression, inflammation, metabolic factors, medications and disability are likely to contribute to the development of RA fatigue in varying degrees[1]. Elevation in pro-inflammatory cytokine levels leads to higher levels of fatigue in RA[2]. A significant role is played by interleukin 6 (IL-6) in the pathogenesis of RA and promotion of fatigue. The positive effects of IL-6 inhibition on symptoms of fatigue in patients with moderate-to-severe RA, have been assessed by studies but results were conflicting and none were done in Indian patients with RA. This study was aimed to evaluate the occurrence of fatigue as measured by BRAF-MDQ score and its correlation with serum interleukin-6 level.

Material and methods: This study was done in the Department of Medicine , Post-graduate Institute of Medical Education and Research, Dr Ram Manohar Lohia Hospital, New Delhi, between 1st November 2016 and 31st March 2018 and included 40 patients with RA diagnosed according to the 2010 ACR-EULAR criteria. Disease activity was assessed using erythrocyte sedimentation rate (ESR), 28 joint disease activity score (DAS28) and Health assessment questionnaire (HAQ). Serum IL-6 level was measured in all patients and fatigue was assessed with the Bristol Rheumatoid Arthritis Fatigue Multidimentional Questionnare (BRAF-MDQ).

Conclusion: Fatigue scores were high in patients with RA and should be measured using simple questionnaires. There is direct, positive and statistically significant correlation between fatigue score (BRAF-MDQ score) and serum interleukin-6 levels in patients with rheumatoid arthritis. Fatigue was also high in patients with higher ESR levels and CRP positivity.

Introduction

Rheumatoid Arthritis (RA) is the commonest form of chronic polyarticular inflammatory arthritis characterised by persistent synovial inflammation, bony erosions and progressive articular destruction, causing varying degrees of physical disability[3]. The disease is characterised by periods of disease flare and remissions. The prevalence of rheumatoid arthritis in india (0.75%) is similar to that reported in the white population from Manchester, UK (0.8%)[4].

The health-related quality of life in patients with RA is significantly reduced by the pain, fatigue and loss of bodily function[5]. Fatigue, as a symptom, in patients with RA is not very commonly assessed by clinicians. It is a subjective feeling of low vitality that disrupts daily functioning[6]. At different times pain, stress, depression, inflammation, metabolic factors, medications and disability are likely to contribute to the development of RA fatigue in varying degrees[7]. Disease activity and excessive inflammation have been postulated to contribute significantly to fatigue in RA[8]. International consensus strongly recommends that RA related fatigue should now be measured in RA studies using a validated instrument[7]. Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF-MDQ) is one such scoring instrument which was developed to assess the overall experience and impact of RA fatigue and its different dimensions[9,10].

In RA, numerous cytokines are present, both in blood and in synovial joints, and hence the cytokine network is complex[1]. Elevation in pro-inflammatory cytokine levels leads to higher levels of fatigue in RA[2]. A significant role is played by interleukin 6 (IL-6) in the pathogenesis of RA and promotion of fatigue[11]. Hypothalamic-pituitary-adrenal axis abnormalities have been linked to the development of fatigue in many diseases including RA[12]. The TAMARA[13] and OPTION studies including rheumatoid arthiritis patients[14] reported positive effects of Tocilizumab (a humanised anti IL-6 receptor neutralising antibody) on fatigue. Our study was planned to assess the occurrence and level of fatigue by BRAF-MDQ score and to correlate the level of fatigue with IL-6 levels and with ESR and CRP, in patients of RA.

Material and methods

This was a cross-sectional, observational study conducted in the outpatients and inpatients Depatment of Medicine,

**Professor, **Senior Resident, Department of Medicine, ABVIMS and Dr Ram Manohar Lohia Hospital, Baba Khrak Singh Marg, New Delhi - 110 001.*

Corresponding Author: Dr Yogita Sharma, Senior Resident, Department of Medicine, ABVIMS and Dr Ram Manohar Lohia Hospital, Baba Khrak Singh Marg, New Delhi - 110 001. Tel: 9582029225, E-mail: dr.yogita12@gmail.com.

Dr Ram Manohar Lohia Hospital, New Delhi and included forty patients with RA. Persons of either gender diagnosed with RA by ACR/EULAR 2010 criteria[15] and age more than 16 years were included in the study. The exclusion criteria were Overlap syndromes (patients who also have another diagnosed rheumatological disease), chronic hepatic diseases, kidney diseases, diabetes mellitus and malignancy. After being approved by the institution ethics committee an informed consent was taken from all patients before the beginning of study.

Demographic data and disease history regarding onset, duration, course, progression and medications were obtained from the patient. A general physical and thorough clinical examination of the musculoskeletal system was carried-out. Disease activity was measured using the 28 joint disease activity score (DAS28)[16] which was performed bilaterally on the shoulders, elbows, wrists, metacarpophalangeal, proximal interphalangeal and knee joints. Formula used for calculating the score was DAS 28 score = 0.56 x "tender joint count + 0.28 x "swollen joint count + 0.70 x ln [ESR] + 1.14 x (patient's global assessment on a scale of 1 - 100, measured using Visual analog scale). > 5.1 = High disease activity, > 3.2 – ≤ 5.1 = Moderate disease activity , ≤ 3.2 = Low disease activity, < 2.6 = Remission. Each patient completed a Health Assessment Questionnaire (HAQ). A modified version of the MDHAQ adapted for clinical use in Indian patients was developed and validated by Kumar *et al* in 2002[17]. This questionnaire was used in the present study. Each patient was assessed with the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF-MDQ)[10]. The 20 item BRAF-MDQ has 4 distinct dimensions: the physical, living, cognition and emotion dimensions. The physical dimension contains a numerical rating scale and questions on frequency and duration of fatigue, but the response options to all questions of other dimensions are scored as 0 - 3 (where 0 = not at all, 1 = a little, 2 = quite a bit, and 3 = very much). Simple summation yields a global BRAF-MDQ score of 0 - 70 (with higher scores indicating worse fatigue), whereas the score for each dimension is different due to the varied number of questions (0 - 22 for physical, 0 - 21 for living, 0 - 15 for cognition, and 0 - 12 for emotion). Laboratory investigations were carried-out for each patient and included ESR using the standard Westergren method[2] C-reactive protein (CRP)[18], spectrophotometrically on Vitros analyser and serum IL-6 level using the enzyme-linked immunosorbent assay (ELISA), (the Diaclone IL-6 ELISA kit was used). Categorical variables are presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Quantitative variables were compared using Independent T test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups and ANOVA/Kruskal Wallis test between more than two groups. Qualitative variables were correlated using Chi-Square test. Pearson correlation co-efficient/Spearman rank correlation co-efficient was used to assess the association of various parameters with each other. Univariate and multivariate linear regression was used to find out the significant risk factors affecting BRAF MDQ. A p value of < 0.05 was considered statistically significant.

The data were entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Our study included 40 patients with RA whose mean age was 38.45 years. There were 31 (77.5%) women and 9 (22.5%) men. The duration of symptoms ranged from 2 months to 7 years, with a mean duration of 2.31 years. Erythrocyte sedimentation rate ranged from 2 to 90 mm in first hour, with mean ± SD of 33.45 ± 20.16 mm in first hour. C-reactive protein was positive in 23 (57.50%) and negative in 17 (42.50%) patients in our study population. 29 (72.50%) patients were RF positive and 11 (27.50%) were RF negative. Mean ± SD Anti CCP value was 117.18 ± 107.96. Most patients had low or moderate disease activity by DAS28. Scores ranged from 0.51 to 6.1, with a mean of 3.21 and standard deviation of 1.26. HAQ score ranged from 0.5 to 2.67 with a mean of 1.75 and a standard deviation of 0.61.

Serum levels of IL-6 in the study population ranged from 1.95 to 342.5 pg/ml with a mean of 37.92 pg/ml and standard deviation of 75.29 pg/ml. Total fatigue score ranged from 25 to 65 with mean of 44.1 and standard deviation of 8.33. Out of the four dimensions of BRAF-MDQ score, physical dimension ranged from 4 to 22 with mean ± SD of 16.65 ± 3.5, living dimension ranged from 4 to 19 with mean ± SD of 10.45 ± 3.67, cognitive dimension ranged from 3 to 12 with mean ± SD of 8.15 ± 2.21 and emotional dimension ranged from 4 to 12 with mean ± SD of 9.1 ± 2.47.

Spearman's rank correlation co-efficient was used to find correlation between BRAF-MDQ score and IL-6 levels, ESR, and BMI. Levels of serum IL-6 were found to be very strongly correlating with BRAF-MDQ score, with p value of < 0.0001 and a correlation co-efficient of 0.821 (shown by scatter plot in Fig. 1).

It was found that higher fatigue score was reported in patients with high ESR levels with statistically significant p value of 0.015 and correlation co-efficient of 0.383. No statistically significant correlation was found between BMI and fatigue score with a p value of 0.978 and correlation co-efficient of 0.004. No statistically significant correlation was found between BRAF-MDQ score and age of the

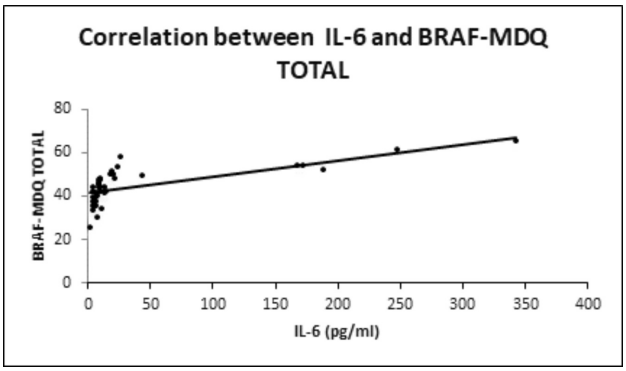

Fig. 1: *Correlation between IL-6 and BRAF-MDQ score.*

patients or duration of RA using Pearson's correlation co-efficient as depicted by p values of 0.6333 and 0.5898 respectively. Independent T-test was used to find correlation of BRAF-MDQ score with CRP positivity, haemoglobin levels and gender of the study population. Patients with positive CRP were found to have higher fatigue score as compared to CRP negative patients and this was statistically significant with p value of 0.01. But no such correlation was seen between anaemia or gender of the patients with fatigue score.

Univariate regression analysis was performed to assess the relationship between BRAF-MDQ score as outcome measure with variables ESR, DAS28, IL-6, Anti-CCP, and CRP. Thia was found to be statistically significant for all the above variables except Anti-CCP levels (Table I).

Table I: Univariate linear regression for BRAF-MDQ TOTAL.

	Unstandardised Co-efficients		Standardised Co-efficients	P value	95.0% confidence interval for B	
	B	Std. error	Beta		Lower bound	Upper bound
ESR	.131	.064	.317	.046	.002	.260
DAS-28	2.568	.992	.387	.014	.559	4.576
IL-6	.076	.013	.685	< .0001	.049	.102
ANTI-CCP	.004	.013	.049	.766	-.022	.029
CRP	6.721	2.469	.404	.010	1.723	11.719

Multivariate linear regression analysis was done to assess ESR, DAS28, IL-6, and CRP as independent predictors of fatigue as measured by BRAF-MDQ score. ESR (p = 0.373), DAS28 (p = 0.851), CRP (p = 0.116) were not significantly independent predictors of fatigue score (BRAF-MDQ) while IL-6 with a p < 0.0001 had a strong correlation with BRAF-MDQ. So after adjusting for confounding factors, IL-6 was the only factor affecting BRAF-MDQ score in patients with rheumatoid arthritis.

Discussion

Fatigue is a frequent symptom of RA. Patients regard it as an important, neglected facet of the disease. It is complex and multicausal. It results from the interaction between disease, cognitive, behavioural factors and personal life issues and so its assessment and measurement is complex. Elevation in pro-inflammatory cytokines is capable of promoting fatigue in RA. IL-6 is one of the cytokines which play a significant role in the pathogenesis of RA and the promotion of fatigue[6, 7, 18,1,19].

Serum levels of IL-6 were raised in our study and it was comparable with the previous studies as shown in the Table below.

Study name	IL-6 levels
Our study	Mean 37.92 ± 75.29 pg/ml
Chung *et al*[20]	Mean 41.76 ± 20.28 pg/ml
by Madhok *et al*[21]	Median 55 IU/ml
by Lacki *et al*[22]	Mean 39 pg/ml
Helal *et al*[13]	Mean of 35.0 ± 21.2 pg/ml

It is concluded that patients with higher fatigue score had higher IL-6 serum levels. Our results were comparable to those of Helal *et al*[13]. They found a strong correlation between BRAF-MDQ score and serum IL-6 concentration with r = 0.947, p < 0.001. We found that fatigue was higher in patients with higher DAS28 scores, with correlation co-efficient 0.337 and p value = 0.034. In a study by Pinals *et al*[23] a significant correlation was found between fatigue and disease activity and the authors emphasised that lack of fatigue was a feature of clinical remission in RA. In contrast in an Egyptian study[13], there was no significant correlation between BRAF-MDQ score and DAS28 score (r = 0.174, p = 0.358). In our study it was found that higher fatigue scores were measured in patients with a higher ESR with p value = 0.015 and a correlation co-efficient of 0.383 and also in patients who were CRP positive. These findings are similar to those of the study done by Helal *et al*[13] where BRAF-MDQ score in patients with RA correlated positively with ESR (r = 0.509, p < 0.001) and CRP (r = 0.411, p = 0.005). However in a study done by Bergman *et al*[24] there was only a weak association between fatigue and ESR. Another study done by Riemsma *et al*[25] found that ESR did not contribute to fatigue. In a study done by Van Hoogmoed *et al*[26], pain, disability, depression, and low self-esteem were associated with greater fatigue, but inflammatory indices were not correlated with fatigue severity. Wirnsberger *et al*[27] reported that patients with RA with elevated CRP levels had low levels of energy and more fatigue. No significant correlation was found between BRAF-MDQ score and age of the patients (p =

0.6333), duration of disease (p = 0.5898), haemoglobin levels (p = 0.997) or gender of the patients (p = 0.418) in the present study. Helal *et al*[13] too did not find any significant relationship between BRAF-MDQ score and age, gender of RA patients or duration of the disease. Using a multivariate approach, Riemsma *et al*[25] also found that pain, low efficacy expectations, and problematic support explained 37% of the variance in fatigue, while ESR, rheumatoid factor and haemoglobin did not contribute to fatigue. Huyser *et al*[28] also reported that the best predictor of fatigue was being a female. However, our study did not find any such correlation. Madhok *et al*[21] also confirmed that serum IL-6 did not correlate with age, gender and duration of RA.

This is one of the few studies assessing fatigue in Indian patients of rheumatoid arthritis and correlating it with high serum IL-6 levels. However major limitations were small sample size, absence of controls, less number of men. So in future this study may be extended to include more number of patients.

Conclusion

In our study, BRAF-MDQ scores for fatigue in patients with RA were found to be high and had a significant correlation with serum IL-6 concentration. Higher fatigue scores were observed in patients with raised inflammatory markers, ESR and CRP. So in patients of RA, fatigue should be evaluated in all patients. Reduction in serum IL-6 levels may help reduce fatigue in these patients. Hence optimal treatment of RA-related fatigue should be included in the management of patients of RA, in conjunction with standard medical management.

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