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Fatigue and health-related quality of life in patients with pulmonary sarcoidosis treated by oral corticosteroids

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Abstract. *Background:* It is not clear how well sarcoidosis-associated fatigue improves with definitive therapy. *Objective:* To evaluate improvement in fatigue in patients of sarcoidosis receiving oral corticosteroid therapy, and correlate it with clinical recovery and change in health-related quality of life (HRQL). *Methods:* We studied 51 newly diagnosed adult patients of pulmonary sarcoidosis. Sarcoidosis Health questionnaire (SHQ) was used to assess HRQL. Fatigue was evaluated using Fatigue Assessment Scale (FAS). All patients received six month treatment with oral prednisolone, and SHQ and FAS were administered before initiation and after completion of treatment. Baseline and post-treatment scores were compared and a 4-point change in FAS scores considered clinically significant. *Results:* All patients improved clinically and radiologically with therapy. Body aches, however, persisted in 12 of 28 (42.9%) patients having this symptom at baseline. 33 patients (64.7%) had pre-treatment fatigue (FAS >=22), of which seven (13.7%) were severely fatigued (FAS score >=35). Of them 21 (63.6%) and 4 (12.1%) patients respectively showed improvement and deterioration in FAS score by >4 points. Only five of 18 patients with baseline FAS score <22 also showed >4 point score increment after treatment, and four of them developed fatigue during therapy. All patients with baseline severe fatigue improved. Overall, FAS scores, and all SHQ domain scores, significantly improved with treatment. *Conclusions:* Both fatigue as well as HRQL improved significantly, and largely parallelly, in patients treated for sarcoidosis. Persistence of fatigue, or new onset fatigue, may be encountered during treatment, possibly as an adverse effect of corticosteroid therapy. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 124-129)*

Key words: fatigue, health status, India, quality of life, questionnaires, sarcoidosis

Introduction

Fatigue is one of the commonest systemic manifestations reported in sarcoidosis, although it is still under-recognized in clinical practice (1). The pathogenesis of fatigue is complex and largely remains unknown, although systemic inflammation, sleep disturbances, depression and small fibre neuropathy may play some role (2). Neither radiography nor pulmonary function testing reflects the extent or severity of fatigue in sarcoidosis patients (3). Fatigue is best assessed using specific questionnaires. Although several fatigue instruments are available, Fatigue Assessment Scale (FAS) is the only fatigue questionnaire validated in sarcoidosis (4). Fatigue is negatively correlated with health-related quality of life (HRQL) and overall health status, and appears to be the best predictor of HRQL in these patients (2, 5). It is not entirely clear how fatigue responds to treatment for sarcoidosis. Only few longitudinal studies have looked at temporal changes in fatigue;

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however all patients did not receive immunosuppressive therapy in these studies (6, 7). These data suggest that sarcoidosis-associated fatigue may either improve or worsen with therapy (7). Few longitudinal studies have reported improvement in fatigue among patients of refractory sarcoidosis treated with tumour necrosis factor-alpha inhibitors (8, 9). Other studies have documented residual fatigue in patients treated for sarcoidosis, especially those receiving immunomodulatory therapy (10-13).

There is no data on the prevalence of fatigue, or its response to treatment, in Indian patients with sarcoidosis. We undertook this study to evaluate improvement in fatigue, if any, in patients of pulmonary sarcoidosis receiving oral corticosteroid therapy, and to correlate change in severity of fatigue with (a) clinical recovery, and (b) change in the HRQL, after completion of treatment.

Methods

Consecutive adult patients (aged >15 years) of newly diagnosed pulmonary sarcoidosis, seen at our Chest Clinic over a one-year period, were eligible for enrolment. Subjects with any major comorbidity (such as psychiatric illness, severe cardio-respiratory disease or any pre-existing musculoskeletal disorder, or malignancy) were not included into the study. The study protocol was approved by the Institute Ethics Committee, and written informed consent was obtained from all participants prior to inclusion.

As part of the diagnostic work-up, all patients underwent thoracic CT scan and flexible bronchoscopy. Bronchoscopic procedures included transbronchial needle aspiration of mediastinal lymph nodes, endobronchial biopsy and bronchoscopic lung biopsy as per the standard protocol followed at our institute, and the clinical specimens were submitted for both pathologic examination and mycobacterial culture (14). Sarcoidosis was diagnosed based on (a) compatible clinical symptoms and thoracic radiology, (b) demonstration of non-caseating granulomas on transbronchial needle aspiration of mediastinal lymph nodes and/or bronchoscopic lung biopsy, and (c) exclusion of tuberculosis (15). All patients received oral prednisolone initially as a single daily dose of 0.75 mg/kg for a month. Corticosteroids were tapered and stopped over the next five months (0.5 mg/kg/day for a month, 0.5 mg/kg/day for three months, 10 mg/day for a month, and 5 mg/day for a month).

Information on personal details (residence, age, gender, etc.), clinico-radiologic details, and laboratory test results was gathered at inclusion. All patients were scheduled for two assessments. The first was conducted at the time of initiating corticosteroid therapy, and second at six months (after completion of treatment).

A Hindi adaptation of Fatigue Assessment Scale (FAS) was used to identify and quantify fatigue. FAS is a ten-item questionnaire, with five questions reflecting physical fatigue and five questions for mental fatigue (16). Patients self-completed the questionnaire at both assessments and all questionnaire items were rated on a five-point Likert scale (1, never to 5, always). The response scores were summated to get a total score, which ranged from 10-50. FAS scores >=22 and >=35 implied fatigue and severe fatigue respectively (4). A four-point change in FAS scores after therapy was considered clinically significant (17).

A Hindi adaptation of a disease specific tool - the Sarcoidosis Health questionnaire (SHQ) - was used to assess HRQL. SHQ is a 29-item questionnaire, assessing HRQL in three domains - Daily Functioning, Physical Functioning, and Emotional Functioning (18). Patients self-completed the questionnaire at both assessments, and rated all questionnaire items on a seven-point Likert scale. The response scores were summated to get the three domain scores and a total score, which ranged from 1-7, with higher scores reflecting better HRQL.

Both FAS and SHQ were linguistically translated into Hindi from their original English version prior to start of the study. This translation was then back-translated to English, and compared to the original questionnaires to verify that the individual items conveyed the same meaning.

Besides change in fatigue and HRQL, improvement in symptoms was subjectively assessed using patient feedback. Baseline and end-of-treatment radiographs were compared to assess radiologic recovery with treatment. Baseline and post-treatment assessments were compared using Fisher's exact test (for categorical variables) and Wilcoxon's signed rank test (for scalar variables). Pearson's coefficient was used to assess correlations.

Results

We studied 51 newly diagnosed patients of pulmonary sarcoidosis (23 women and 28 men) during the study period. All patients were symptomatic, and eight also showed additional extrapulmonary manifestations. Demographic and clinical profile of the study population is summarized in Table 1.

Prevalence of fatigue was second only to the prevalence of cough. 33 patients (64.7%) had pre-treatment fatigue (FAS >=22), of whom seven (13.7%) had severe fatigue (FAS score >=35) (Fig 1). Baseline FAS scores were significantly and negatively correlated with daily functioning, physical functioning, emotional functioning and total SHQ scores (Pearson's correlation coefficients -0.438, -0.445, -0.420, and -0.508 respectively, p <0.01 for all), but not with lung function (Pearson's coefficient with percent predicted forced vital capacity -0.141, p 0.324). More patients coming from rural areas had fatigue as compared to those from urban locations (Table 2). All eight patients with extrapulmonary manifestations had fatigue, and showed poorer SHQ and FAS scores (Table 2). FAS scores were also worse among patients with stage 2 disease on chest radiography. However, baseline SHQ and FAS scores were similar for men and women, and those with or without restrictive defects on pulmonary function testing (Table 2).

Patients received a median dose of 45 mg prednisolone daily as initial treatment. All patients showed clinical and radiological improvement with therapy. Body aches, however, persisted in 12 of 28 (42.9%) patients having this symptom at baseline. Overall, FAS scores, and all SHQ domain scores, significantly improved with treatment (Table 3). Among those with pre-treatment fatigue, 21 (63.6%) and 4 (12.1%) patients respectively showed improvement and deterioration in FAS score by >4 points after completion of treatment. Only five of 18 patients with baseline FAS score <22 also showed >4 point score increment

Table 1. Demographic and clinical parameters of study population

Age (years), mean ±SD		44 (±10)
Gender	Men	28 (54.9%)
	Women	23 (45.1%)
Residence	Urban	31 (60.8%)
	Rural	20 (39.2%)
Tobacco smoking	Nonsmoker	44 (86.3%)
	Current smoker	7 (13.7%)
Symptoms/signs	Cough	37 (72.5%)
	Breathlessness	30 (58.8%)
	Fever	22 (43.1%)
	Extrapulmonary manifestations	8 (15.7%
Scadding stage	1	32 (62.7%)
	2	19 (37.3%)
PPD skin test	Non-reactive	41 (80.4%)
	1-10 mm	8 (15.7%)
	>10 mm	2 (3.9%)
Body weight (kg)		65 (±11)
Body mass index (kg/m^2)		25.4 (±3.9)
FVC (% predicted), mean ±SD		85 (±14)
FEV1 (% predicted), mean ±SD		85 (±16)
Restrictive defect on spirometry		10 (19.6%)

FEV1 Forced expiratory flow in first second; FVC Forced vital capacity
All values are expressed as number (percentage) unless otherwise stated

Table 2. Impact of patient characteristics on baseline Sarcoidosis Health Questionnaire (SHQ) and Fatigue Assessment Scale (FAS) scores.

		SHQ Mean±SD	FAS Mean±SD	FAS >=22 No. (%)
Gender	Men	4.93±0.74	24.57±6.57	17 (60.7%)
	Women	4.51±0.86	26.43±9.15	16 (69.6%)
Residence	Urban	4.80±0.87	24.48±8.19	16 (51.6%)
	Rural	4.66±0.75	26.85±7.15	17 (85.0%)*
Extrapulmonary manifestations	No	4.87±0.81	23.53±6.17	25 (58.1%)
	Yes	4.08±0.54*	35.50±8.33*	8 (100%)*
Scadding stage on radiography	1	4.84±0.89	23.03±5.16	20 (62.5%)
	2	4.57±0.67	29.42±9.83*	13 (68.4%)
Restrictive defect on spirometry	Yes	4.45±0.83	26.20±7.93	8 (80.0%)
	No	4.81±0.81	25.22±7.87	25 (61.0%)

* p <0.05

Table 3. Comparison of scores before and after treatment

	Pre-treatment	Post-treatment	P value
Fatigue Assessment Scale			
- Bothered by fatigue	2 (2-3)	2 (2-2)	0.010
- Getting tired very quickly	3 (2-4)	2(1-3)	0.006
- Not doing much during the day	3 (2-4)	3 (2-3)	0.792
- Enough energy for everyday life	3 (2-4)	4 (3-4)	0.004
- Physical exhaustion	3 (2-4)	2 (2-3)	0.002
- Problems starting things	2 (2-4)	2 (1-3)	0.012
- Problems thinking clearly	1 (1-3)	2 (1-2)	0.680
- Lack of desire to do anything	2 (1-3)	2 (1-3)	0.793
- Mental exhaustion	2 (1-3)	2 (1-3)	0.336
- Lack of concentration	3 (2-4)	4 (3-4)	0.001
- TOTAL	24 (19-30)	21 (17-27)	0.004
Sarcoidosis Health Questionnaire			
- Daily Functioning domain	4.85 (4.00-5.31)	5.31 (4.62-5.85)	0.003
- Physical Functioning domain	4.67 (4.00-5.17)	5.33 (4.67-5.67)	0.007
- Emotional Functioning domain	4.80 (3.90-5.50)	5.30 (4.90-5.90)	0.001
- TOTAL	4.83 (4.21-5.41)	5.28 (4.59-5.83)	<0.001

Values expressed as median (interquartile range)

after treatment, and four of them developed fatigue during therapy (Figure 1). All patients having severe fatigue before starting therapy improved. Significant shifts in FAS scoring were more often observed for items relating to physical, rather than mental, fatigue (Table 2).

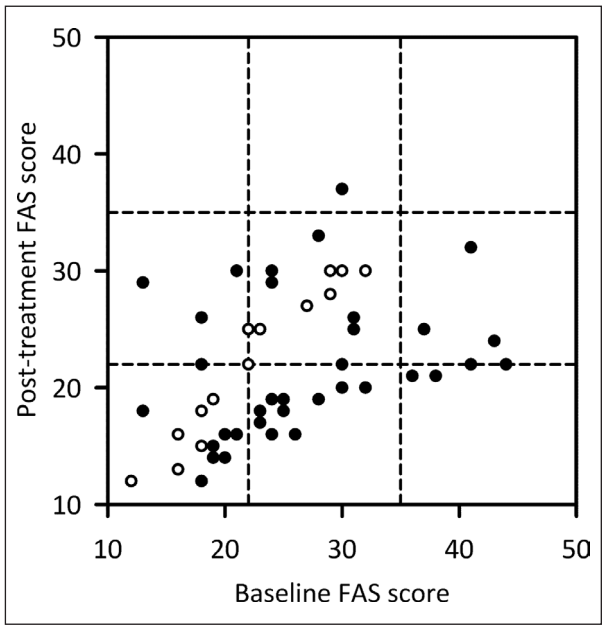

Fig. 1. Fatigue Assessment Scale (FAS) scores before and after treatment. The dotted reference lines indicate presence of fatigue (FAS >=22) and severe fatigue (FAS >=35). Filled circles represent patients with a significant change in FAS score (>=4 points) with therapy, and hollow circles represent those with a stable FAS score (<4 point change)

Of nine patients with clinically significant deterioration in FAS scores, six, five and five patients respectively showed marginal worsening in the SHQ Daily Functioning, Physical Functioning, and Emotional Functioning domain scores also.

Discussion

To the best of our knowledge, this is the first study to specifically report on fatigue in Indian patients of pulmonary sarcoidosis, and its response to corticosteroid therapy. Using the FAS, we found that majority (64.7%) of the patients included in this study had fatigue. These figures are largely similar to several multinational studies where up to 85% patients with symptomatic sarcoidosis have reported fatigue assessed through various definitions (1). The main strength of this study is a longitudinal design that was specifically framed to assess change in fatigue with oral corticosteroid treatment. Hence we were able to not only generate cross-sectional data on prevalence of pre-treatment and residual (post-treatment) fatigue, but also provide specific information on the direction of change in fatigue in these patients. Previous studies reporting follow-up data evaluated a mix of patients, only some of whom received corticosteroid therapy (6, 7). All patients in our study received oral corticosteroids under a uniform protocol.

Despite clinico-radiologic improvement among all patients studied, we noted that fatigue did not significantly improve in all. Only 63.6% patients with fatigue before starting treatment showed significant improvement in FAS scores. Nine patients (four with fatigue, and five without) worsened significantly with corticosteroids. Although previous studies have implicated such therapy with development of fatigue, none have reported on the incidence of new-onset fatigue among patients receiving immunomodulatory therapy. A recent study found that sarcoidosis patients receiving >500 mg corticosteroids in the previous year had significantly worse fatigue scores using Sarcoidosis Assessment Tool (19). All our patients received a much higher cumulative dose over their six-month treatment. Another study showed that even after adjusting for other covariates, use of immunomodulator therapy was a significant predictor of fatigue (10). Current prednisolone usage was associated with higher fatigue scores in American, but not Dutch, patients in another study (13). More severe physical, but not mental, fatigue was reported among patients receiving immunomodulatory therapy in one study (12). Because fatigue appeared or worsened in some of our patients despite overall favourable clinical response to treatment, we believe that use of corticosteroids may have been a major contributory factor. It is well known that patients on chronic corticosteroid therapy can experience adverse effects such as myopathy, depression, and sleep disturbances, all of which can contribute to a feeling of fatigue.

Some investigators have previously noted worse HRQL among women with sarcoidosis, as compared to men (20, 21). However, we did not find any such gender differences. Previous cross-sectional studies have found that fatigue correlates inversely with HRQL; however, these studies used generic HRQL instruments (2). We also found that pre-treatment fatigue was inversely related to all HRQL, assessed using a sarcoidosis-specific questionnaire, across all domains. In addition, we also noted that most patients who developed fatigue while on treatment also showed a parallel worsening of HRQL. The number of patients is small to derive any firm conclusions, but we feel that our findings provide additional evidence that fatigue in sarcoidosis is a major determinant of HRQL in these patients.

A limitation of the current study is that all patients were studied at a tertiary referral centre, had predominantly pulmonary sarcoidosis, and were all candidates for receiving oral corticosteroid therapy. Thus our findings may not be generalizable to sarcoidosis patients in other settings or in general. Several sarcoidosis patients do not require definitive therapy, and the prevalence and temporal course of fatigue may be different in these patients. Owing to a referral bias at our institute, we encounter very few such patients, and inclusion of matched controls as part of this study was therefore not feasible. A longitudinal design however ensured that each patient acted as his/her own control. A randomized controlled design to specifically dissect the role of corticosteroids in improving fatigue, vis-à-vis its spontaneous resolution, may not be justified in view of denial of therapy to deserving patients, or administration of treatment to those who do not need it. It appears quite likely that the improvement in fatigue observed in our patients was a result of corticosteroid therapy, since untreated patients are known to remain chronically fatigued, despite improvement in other clinical and radiologic parameters. The DSS study, for instance, showed prevalence of fatigue of about 80%, mainly in 'chronic' sarcoidosis patients (22). Two recent studies have shown no clear difference in prevalence of fatigue at baseline and at followup among sarcoidosis patients (6, 7). We also did not specifically treat fatigue in any patient. Previous investigators have advocated pharmacotherapy targeted towards amelioration of fatigue in these patients, using agents such as D-methylphenidate or R-modafinil (23, 24).

We conclude that fatigue is a frequent manifestation of sarcoidosis, as well as a determinant of HRQL, in north Indian patients. Both fatigue and HRQL improve significantly, and largely parallelly, in patients receiving oral corticosteroid therapy, though fatigue may persist even after completion of treatment. Persistence of fatigue, or new onset fatigue, during therapy may be an adverse effect of corticosteroids.

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