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The Relationship between Physical Activity, Functional Performance, and Fatigue in Sarcoidosis

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Aims and Background

Sarcoidosis patients report debilitating fatigue, clustered with pain, dyspnea, depression and anxiety (Baughman *et al.*, 2012). Investigations into clinical measures such as questionnaires, pulmonary function tests, exercise tests, metabolic measures, and inflammatory markers have been attempted to quantify sarcoidosis-related fatigue, but no clinical or physiological parameter has been shown to be a reliable predictor of fatigue (De Vries *et al.*, 2004). Our study recognized this gap and explored the fatigue symptoms, along with free-living physical activity (level of physical activity within one's physical limitation and in one's own environment), skeletal muscle strength, functional performance, and depressive symptoms of sarcoidosis patients compared to sedentary healthy controls.

Design

This prospective, observational, pilot study enrolled 14 patients with pulmonary sarcoidosis and 13 age-, sex-, and race-matched, sedentary controls by convenience sampling. The study was conducted at the National Institutes of Health (NIH), Clinical Research Center, Bethesda, Maryland, USA from December 2008 to August 2009. Biopsy-confirmed sarcoidosis patients without cardiac or neurosarcoidosis referred for enrollment in a screening protocol 08-NR-0132 (NCT00677157) were included. Participants unable to sign an informed consent and/or unwilling/unable to cooperate with study procedures were excluded.

Sedentary controls, who report not doing any moderate and/or vigorous physical activity for longer than 5 minutes a day were enrolled under protocol 09-NR-0131 (NCT00888563). These controls were >18 years and able to sign the informed consent and cooperate with study procedures. Protocols were approved by the Combined Neuroscience Institutional

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1. substantial contributions to conception and design of, or acquisition of data or analysis and interpretation of data,
2. drafting the article or revising it critically for important intellectual content, and
3. final approval of the version to be published.

Review Board, NIH. Following written informed consent, all study participants completed questionnaires before other clinical measures were obtained.

Methods

Demographic and clinical information were obtained from medical records. Participants completed the Fatigue Assessment Scale (FAS), a 10-item questionnaire with 5 questions on physical fatigue and 5 questions on mental fatigue that has been validated in sarcoidosis with internal consistency of 0.91 (Michielsen *et al.*, 2005). The 21-item Hamilton Depression Rating Scale (HAM-D) which was validated in another fatigue study, screened participants for depressive symptoms (Erin *et al.* 2006), during review of medical history and physical exam.

In addition to fatigue and depression, the following outcome measures were obtained: (1) free living physical activity was measured by actigraphy for 3 consecutive weekdays in the participant's own environment using the Actical® (Mini Mitter Co., Inc., Bend, OR); (2) isometric skeletal muscle strength was measured on the dominant hand using a hand-held dynamometer (The Computer Source, Gainesville, GA), which measures maximum voluntary contraction (MVC) in kilograms; (3) functional performance was measured by the 6-minute walk test (6MWT) conducted in an indoor, 30 meter, leveled corridor. The 6MWT was conducted according to the 2002 American Thoracic Society guidelines, which collects the distance walked in meters, and subjects were asked of their fatigue and dyspnea levels pre- and post-test based on the 0 to 10 Borg scale, where 0 =no fatigue/dyspnea and 10 =very, very severe fatigue/dyspnea. All measures, except for the Actical® which was taken home by the participant, were obtained during one study visit in an outpatient setting.

Descriptive statistics defined the demographic and clinical characteristics of the sample. Univariate two-sample t-tests were used to compare group means. Statistical analyses were performed using the Statistical Analysis System (SAS) version 9.2 (SAS Institute Incorporated, Cary, NC). Missing data were not imputed. A two-tailed *p*-value of 0.05 was considered statistically significant.

Results

Sarcoidosis subjects differed significantly from matched controls in mean body mass index (BMI) (sarcoid =34.0±9.0, controls =25.9±3.8, *p*=.01), and C-Reactive Protein levels (sarcoid =3.0±2.5, controls =1.3±1.4, *p*=.04). There were significant differences in physical activity, functional performance, skeletal muscle strength, depression and fatigue scores between sarcoidosis patients and healthy controls as described in table 1. Mean total fatigue (FAS) scores were significantly higher (*p*<.0001) in the sarcoidosis group (27.4±5.7) than in controls (14.2±3.5, *p*<.0001), as well as the depressive symptoms (sarcoid =8.6±5.0, controls =2.5±2.2, *p*<.001). Compared to controls, sarcoidosis patients covered less distance on the 6MWT (sarcoid =502±84, controls =607±77, *p*=.003), reported higher Borg dyspnea pre (sarcoid =1.4±1.2, controls =0.1±0.3, *p*=.001) and post (sarcoid =4.5±2.0, controls =1.2±1.2, *p*<.0001) 6MWT, and higher Borg fatigue pre (sarcoid =2.2±1.8, controls =0.5±1.0, *p*=.01) and post (sarcoid =4.7±2.3, controls =0.9±0.9, *p*<.0001) 6MWT, and have

lower mean physical activity count on the most active 10 hours of the day using actigraphy (sarcoid = 28.3 ± 15.8 , controls = 53.9 ± 25.0 , $p=.03$).

For subset analysis the 14 sarcoidosis subjects were placed into 3 groups based on their fatigue and depression scores. Sarcoidosis subjects with high fatigue (FAS>22) and high depressive (HAM-D>12) symptoms (HFHD, N=3) had a significantly lower aldolase level (mean = 3.0 ± 0.0) than those with high fatigue (FAS>22) and low depressive (HAM-D<12) symptoms (HFLD, N=7, mean = 5.9 ± 2.0 , $p=.01$). HFHD subjects had no significant differences in clinical measures with sarcoidosis subjects with low fatigue (FAS<22) and low depressive (HAM-D<12) symptoms (LFLD, N=4), except for their physical fatigue scores (HFHD mean = 19.7 ± 3.5 , LFLD mean = 1.5 ± 0.5 , $p<.001$). Mental fatigue scores did not differ among the three groups.

Conclusions

The study findings are clinically relevant because it suggests that sarcoidosis subjects had higher BMI, were more fatigued, more depressed, more dyspneic, were less physically active, and had lower physical performance than their age-, race-matched controls, which can all be clinically addressed through rehabilitative therapies. Although the sample was small, aldolase levels appear to delineate fatigued sarcoidosis subjects with different levels of depressive symptoms. This is consistent with a previous study which demonstrated that mental fatigue induced a decline in plasma amino acids (Mizuno *et al.*, 2007). A major limitation of the study is the inability to match the BMI between sarcoidosis subjects and controls. This is a new finding and further investigation is warranted to understand the mechanisms that delineate sarcoidosis-specific fatigue from fatigue associated with depression.

Relevance to Clinical Practice

Our significant findings propose that assessment of physical activity and functional performance in combination with measurement of patient-reported fatigue may offer useful clinical information in the evaluation of fatigue in patients with sarcoidosis. Further, the study findings suggest that management of sarcoidosis-related fatigue can focus on the decline in the patients' physical activity and functional performance.

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What does this paper contribute to the wider global clinical community?

- Fatigue assessment may be enhanced by clinical measures such as actigraphy and the 6-minute walk test.
- When faced with a sarcoidosis patient presenting with fatigue, clinicians should rigorously exclude comorbid conditions known to cause fatigue and make a careful delineation between fatigue related to depression and sarcoidosis-related fatigue, perhaps through tools such as the Hamilton Depression Rating Scale.
- Measures of fatigue may assist in monitoring disease progression or response to therapy.

Table 1

Physical Activity, Functional Performance, Skeletal Muscle Strength, Depression, and Fatigue Scores.

	Healthy Controls N=13	Sarcoidosis Patients N=14	
	Mean (SD)	Mean (SD)	<i>p</i> -value
Free—Living Physical Activity			
Energy Expenditure	1748 (601)	1324 (676)	0.18
Mean Activity - Most Active 10 hours/day	53.88 (24.98)	28.28 (15.84)	0.03 *
Mean Activity - Least Active 5 hours/day	0.34 (0.65)	0.12 (0.20)	0.40
Circadian Rhythm	0.99 (0.02)	0.92 (0.19)	0.26
Intradaily Variability of Rest and Activity	1.35 (0.39)	1.07 (0.28)	0.13
Interdaily Stability of Rest and Activity	0.54 (0.27)	0.50(0.36)	0.79
Functional Performance			
6-minute walk distance (meter)	607 (77)	502 (84)	0.003 *
Borg Dyspnea score – pre 6MWT	0.1 (0.3)	1.4 (1.2)	0.001 *
Borg Dyspnea score – post 6MWT	1.2 (1.2)	4.5 (2.0)	<0.0001 *
Borg Fatigue score – pre 6MWT	0.5 (1.0)	2.2 (1.8)	0.01 *
Borg Fatigue score – post 6MWT	0.9 (0.9)	4.7 (2.3)	<.0001 *
Skeletal Muscle Strength			
Maximum Voluntary Contraction (kilogram)	32.71 (5.68)	26.06 (9.15)	0.08
Depression Scores			
Hamilton Depression Scale score 2.5 (2.2)		8.6 (5.0)	0.0004 *
Fatigue Scores (Fatigue Assessment Scale)			
Physical Fatigue	6.8 (2.2)	15.1 (4.3)	<.0001 *
Mental Fatigue	7.3 (2.0)	12.9 (3.0)	<.0001 *
Total Fatigue	14.2 (3.5)	27.4 (5.7)	<.0001 *

* significant ($p < .05$)

6MWT = 6-minute walk test