Oxygen Consumption Deficits in Patients With Residual Fatigue After Primary Coccidioidomycosis

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Patients with coccidioidomycosis often report prolonged and debilitating fatigue after other evidence of infection has resolved. In this study, we quantify fatigue, muscle weakness, and impaired aerobic capacity in 5 such individuals. A closer examination of the cardiorespiratory system may contribute to a better understanding of underlying mechanisms and potential interventions.

Keywords. coccidioidomycosis; exercise; oxygen; pulmonary; strength.

Coccidioidomycosis (CM), also known as valley fever, is an infection caused by Coccidioides immitis and Coccidioides posadasii, fungi endemic to the southwestern United States and parts of Mexico and Central and South America [1]. Approximately two thirds of infections produce an inconsequential illness and result in life-long immunity to second infections. For those who seek medical attention, most signs and symptoms are self-limited. However, for many patients, convalescence is protracted for weeks to many months because of persistent and debilitating fatigue, even after all other evidence of the infection has resolved and routine examinations are normal [2].

Previous studies addressing fatigue in this population have been limited to subjective reports [3, 4]. In this report, we conducted physiologic measurements (ie, strength, pulmonary function, exercise capacity, gas exchange) in 5 individuals with self-reported fatigue after coccidioidal pneumonia without evidence of hematogenous dissemination. At the time of study, any evidence of active infection had resolved. Our exploratory findings, especially a striking reduction in exercise capacity, indicate that further physiologic studies are very likely to lead to a better understanding of this syndrome and its management.

METHODS

Participants were recruited through 2 physicians (J.N.G., J.E.B.) and 2 physical therapists. Inclusion criteria were a diagnosis of CM [2] ≥6 months earlier, no current evidence of active infection, and ongoing complaints of fatigue without medical explanation (eg, anemia). Exclusion criteria were coexisting cardiac failure, respiratory insufficiency, neuromuscular disease, skeletal fractures, or surgeries within the last 6 months. The Institutional Review Board of Northern Arizona University approved all procedures. The first 5 individuals to meet inclusion and exclusion criteria completed the protocol. Participants were asked to (1) refrain from strenuous exercise, alcohol, and smoking for at least 24 hours before testing and (2) fast and avoid caffeinated beverages for at least 2 hours.

Each participant was asked about time since diagnosis, acute or chronic illnesses, current medications, and routine activities that were stopped because of persistent fatigue. The Patient-Reported Outcomes Measurement Information System ([PROMIS [5]] available through the National Institutes of Health), was used to assess fatigue, sleep disturbance, and “global health”, which estimates perceived physical and mental health. HealthMeasures Scoring Service [5] yielded T-scores and standard error (SE) for each PROMIS instrument.

Measurements of strength were grip strength and the 30-second sit to stand test (30sSTS). Results were compared with published sex- and age-matched predicted values and 95% prediction intervals [6]. Pulmonary function was assessed using open-circuit spirometry to measure forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and FVC/FEV1 [7]. Measurements were compared with lower limits of normal (LLN) and predicted values based on age, sex, height, and race [8]. Submaximal level of functional capacity was assessed with the 6-minute walk test (6MWT); results were compared with predicted distances for a healthy population based on sex, age, height, and weight [9]. Gas exchange was measured using a calibrated Cosmed K4b2 Portable Metabolic Measurement System ([K4b2] COSMED srl, Rome, Italy) and indirect calorimetry during maximal exercise with a progressive graded treadmill protocol. This included a 2-minute warm-up and 6-minute walking bouts at 1.1 and 1.3 minutes/second with no incline and 1.3 minutes/second with a 5% and 10% incline. Heart rate (HR) and rate of perceived exertion ([RPE] Borg 6–20 scale) were recorded during each bout.
Testing was terminated in accordance with American College of Sports Medicine guidelines [10]. Absolute VO2peak values, the highest 30-second rolling average during the last 2 minutes of exercise, were converted to relative VO2peak by normalizing to body mass. Relative VO2peak values were compared with sex- and age-specific predicted values [11] and assigned percentile ranks [10]. Ventilatory efficiency was assessed with minute ventilation/carbon dioxide (VE/VCO2) slope and compared with healthy values (≤30) [12]. Cardiovascular efficiency was estimated using oxygen pulse (O2 pulse), or the ratio of VO2peak/HR [13], and compared with predicted values.

RESULTS

Participants included 4 females, ranging from 52 to 65 years of age, and 1 male, 35 years of age (Table 1). Testing was performed 6 to 84 months after the initial diagnosis of CM. All denied acute or chronic illness, anemia, and current use of medications. Participants reported fatigue for the previous 16 weeks or more and difficulty performing ordinary household (eg, clean house) and recreational activities (eg, hike, walk dog) because of fatigue. As a group, the participants scored within 1 standard deviation of the calibration sample on the Sleep Disturbance and Global Health PROMIS instruments. In contrast, the average T-score for the Fatigue Short Form was 63.44 (SE = 1.68), or >1 standard deviation worse than the calibration sample.

Grip strength (43.0 and 26.9 ± 7.8 kg, male and females, respectively) averaged 85% and repetitions during the 30sSTS (24.0 and 15.3 ± 2.5, male and females, respectively) averaged 73% of predicted values based on sex- and age-matched individuals [6]. Pulmonary function measures, including FVC/FEV1, exceeded the LLN for the 3 participants that completed testing, except that FVC and FEV1 values for the male participants were 4%-5% lower than the LLN. On average, the 6MWT distances were 75% ± 14% of predicted values.

The most striking physiologic abnormality was reduced aerobic capacity measured during maximal exercise. All participants reached steady state and exerted maximal effort (≥85% HRmax, RER ≥1.1, or RPE ≥18 and report of extreme fatigue upon exercise termination) [10]. The VO2peak ranged from 44% to 91% of predicted values; 4 were below an 85% cutoff, and all were below the 10th percentile of a sex- and age-matched population [10] (Table 2). The VE/VCO2 slope ranged from 23.3 to 37.2 with 1 value >30 (Participant 2), and O2 pulse ranged from 8.2 to 16.2 mL/beat with 2 values <85% of age-predicted values (Participants 1 and 4) (Table 2).

DISCUSSION

The purpose of this study was to examine the physiology of patients with persistent fatigue after primary coccidioidal infection. Fatigue was not associated with self-perceived sleep disturbance or global health or with pulmonary function in these subjects. However, participants did exhibit muscle weakness, limited submaximal functional capacity, and, most notably, a diminution of aerobic capacity. To our knowledge, this is the first demonstration of physiologic deficits in this syndrome. Four of the five participants had a VO2peak <85% predicted, and all individual results fell below the 10th percentile of sex- and age-matched reference values [9]. The magnitude of this deficit is much greater than that seen with chronic fatigue syndrome [14] or malignancy [15]. This is particularly concerning given the increased risk for cardiovascular morbidity and all-cause mortality associated with values below the 20th percentile [9].

As mentioned in newly revised guidelines for managing CM [2], the described fatigue syndrome could be the consequence of deconditioning. However, given the chronicity of the fatigue, consistently low VO2peak, especially when combined with abnormal VE/VCO2 slope or O2 pulse, indicates that issues other than deconditioning (eg, ventilatory and cardiac insufficiencies, skeletal muscle metabolic capacity) should be considered [10, 12–14, 16]. Studies that extend upon the trends identified in this study and further explore associated impairments may be informative.

Regardless of underlying mechanism, fatigue has proven to be amenable to therapeutic exercise in various clinical populations [16]. The data provided in this report may serve to focus and guide exercise prescription. The harms and benefits of moderate- to high-intensity aerobic exercise or interval training should be systematically explored in persons experiencing CM-related fatigue.

| Participant | Age (Years) | Sex | Body Mass (kg) | Height (m) | Body Mass Index (kg/m2) | Time since Diagnosis (Months) | Participation Limitations (Participant is unable to…) |
|-------------|-------------|-----|----------------|-----------|-------------------------|-----------------------------|----------------------------------------------------|
| 1           | 52          | F   | 53.1           | 1.57      | 21.4                    | 13                          | Hike, vacuum, travel                                  |
| 2           | 65          | F   | 93.4           | 1.75      | 30.4*                   | 84                          | Walk dog, clean house                                 |
| 3           | 35          | M   | 129.7          | 1.78      | 370*                    | 6                           | Take care of kids                                    |
| 4           | 60          | F   | 72.6           | 1.68      | 25.8                    | 7                           | Unload dishwasher, hike                               |
| 5           | 64          | F   | 572            | 1.52      | 24.6                    | 36                          | Participate in any activity after an 8-hour work day without napping |

*Indicates obesity
There are several limitations in our investigation. As a descriptive paper including only 5 participants, there is no control group, the information gleaned from this study cannot be generalized to all persons experiencing prolonged fatigue after a diagnosis of CM, and causality cannot be determined. Other limitations include heterogeneity of participants in terms of severity and time since diagnosis, incomplete physical fitness testing data, and a lack of information regarding prior fitness.

CONCLUSIONS

Despite these limitations, the physiologic testing as performed here corroborate the validity of the very common subjective complaints of fatigue in CM patients. They also provide practitioners with an approach to obtaining objective evidence to assess workplace limitations/absences and guide appropriate referrals for rehabilitation. Future studies regarding fatigue and CM should (1) include larger sample sizes, (2) investigate potential biological markers and underlying mechanisms, and (3) determine the efficacy of targeted therapeutic interventions.

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