Factors correlated with hypermetabolism in patients with amyotrophic lateral sclerosis[1,2]

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ABSTRACT

Background: Amyotrophic lateral sclerosis (ALS) is a severe disease characterized by neurogenic amyotrophy and degeneration of upper and lower motor neurons. Although ALS patients usually experience reductions in fat-free mass (FFM), hypermetabolism via an undetermined source has also been reported.

Objective: The objective was to clarify the metabolic level of ALS patients.

Design: We measured the resting energy expenditure (REE) of 62 patients (32 men and 30 women) with ALS and investigated the factors correlated with metabolic level. Nutritional evaluation included bioelectrical impedance analysis, indirect calorimetry, and calculation of the body mass index. Neurologic assessment included an evaluation of peripheral and central neurologic deficit. Forced vital capacity was measured and smoking status was noted. A complete blood cell count was made and thyroid hormone and C-reactive protein concentrations were measured.

Results: Patients were hypermetabolic, by an average of ≈10% more than in a reference healthy population. FFM, age, and the neutrophil count were significantly associated with REE. The only variable that contributed to the prediction of REE, REE/Z100 kHz (bioimpedance at 100 kHz), REE adjusted for FFM, or the ratio of measured REE to calculated REE was the neutrophil count, which explained only a small percentage of variance in the multiple regression analysis. Hypermetabolism was not associated with a reduction in respiratory function, tobacco use, hyperthyroidism, spasticity and fasciculation intensities, or infection.

Conclusions: Our study corroborates the surprising finding that ALS patients are hypermetabolic. FFM, age, sex, manual muscular testing, the modified Norris limb score, weight, and an increase in circulating neutrophil counts correlated with the hypermetabolic state. Other factors may play a role in pathophysiologic processes that involve mitochondrial energy production or even sympathoadrenergic activation. *Am J Clin Nutr* 2001;74:328–34.

KEY WORDS Hypermetabolism, amyotrophic lateral sclerosis, ALS, motor neuron disease, leukocytosis

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is the most frequently occurring motor neuron disease. It is a degenerative disease of unknown cause that affects the motor neurons of the cerebral cortex, brainstem, and spinal cord (1). ALS is classified as either bulbar-onset (≈25% of cases), characterized by progressive dysphagia and dysarthria (2–4), or spinal-onset (≈75% of cases), marked by peripheral neurologic features (muscle atrophy, cramps, and fasciculations) and a pyramidal syndrome (spasticity) (5). The typical disease course is characterized by progressive irreversible muscle wasting of the limbs, torso, abdomen, and oropharyngeal muscle regions (5, 6). The average age of patients with ALS is 60 y (7). The prevalence of ALS is 4–8 cases/100 000 and the average incidence is 1.5–2 cases/100 000 annually (8). These values reflect a gradual increase in ALS that has been observed worldwide over the past decade (8). Most often, ALS occurs sporadically, but a familial form is seen in 5–10% of cases. Considering both forms of ALS combined, the median survival is 23–52 mo and the mean survival is 27–43 mo (6). In >80% of cases, death is secondary to respiratory difficulty (5).

During the course of ALS there is often a decline in nutritional status that is frequently inadequately addressed in clinical practice, even though it is a significant and independent prognostic factor in survival (9). Malnutrition is explained by several factors, particularly swallowing difficulties (10), which affect all ALS patients (5, 11) but occur earliest in patients with the bulbar-onset form (12). Constipation also plays a role in malnutrition because it may contribute to appetite loss. Constipation results from involvement of abdominal and pelvic muscles, compounded by limited physical exercise, certain medical treatments, and a diet lacking in fiber (5, 10). Sometimes, problems with salivary secretion—typically pseudo-hypersialorrheal, caused by atony of facial muscles and the inability to swallow saliva (10)—impair the patients' dietary intakes. Psychological distress is common and may favor the development of anorexia (13).

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Finally, a state of hypermetabolism has been described, the origin of which is uncertain (14, 15). This hypermetabolism seems paradoxical because ALS patients often experience significant reductions in fat-free mass (FFM), which is the principal determinant of resting energy expenditure (REE) (14, 16). The initial hypothesis to explain this paradox was that there is an increase in respiratory muscular work to maintain adequate gas exchange (14). The goal of the present study was to clarify the metabolic level of ALS patients and the factors that might account for any metabolic variations observed.

SUBJECTS AND METHODS

Subjects

After giving informed consent, 62 patients aged ≥18 y with probable or definite ALS, according to El Escorial World Federation of Neurolgy criteria (17), were studied prospectively. The subjects were informed of the procedure for indirect calorimetry and all agreed to this evaluation. Nutritional, neurologic, and respiratory assessments and blood sample collections were made on the same day whenever possible.

Nutritional assessment

The nutritional assessment comprised whole body impedance analysis, indirect calorimetry, and measurements of height and weight, from which body mass index (BMI) was calculated [as weight (in cm)/height^2 (in m)]. Patients were weighed in their underwear on an electronic balance that recorded to within 0.1 kg (SECA; Vogel & Halke, Hamburg, Germany) and then their heights were measured with a height gauge that recorded to within 0.2 cm (SECA; Vogel & Halke). Body impedance analysis was performed for ≈10 min while the patients were in a supine position and had an empty bladder if possible; an Analycor3 instrument with surface electrodes was used (Spengler, Paris). The program software automatically provided impedances at 5 and 100 kHz, total body water, FFM, and fat mass. The equations used with the apparatus are unpublished. We previously validated, using the Bland-Altmann method (unpublished observations, 1999), the FFM results obtained with this 2-frequency bioimpedance technique against those obtained with absorptiometry. Indirect calorimetry was performed with a Deltatrac II apparatus (Datex Engström, Helsinki) that was calibrated each morning before the measurements were made. The classic ventilated-hood technique was used according to standard methods (18, 19). Patients with uncontrolled diabetes, renal insufficiency, urinary ketosis, acute respiratory or other infection, or clinically apparent hyperventilation were excluded.

Patients who were included in the study were examined in the morning after fasting overnight for ≥10 h and after resting in a supine or semiseated position for ≥20 min. Measurements were accepted if the results were at a stable plateau for ≥20 min. The measured REE (mREE) was compared with REE obtained from a control population of 31 healthy volunteers and with REE calculated (cREE) by using the Harris-Benedict equations (20).

Current tobacco use was noted but not quantified. A dietary survey was not performed because of the frequent difficulty with communication in this population (21, 22). In the many patients with speech or writing difficulties, dietary information would have been biased or limited to that which could only have been provided by their close relatives. Additionally, it has been observed that ALS patients that are losing weight often overestimate their intake, particularly if they will not accept the possibility of enteral nutrition, which is considered to indicate a worsening of their disease.

Neurologic assessment

Neurologic deficit was quantified by manual muscular testing of all extremities and the neck as defined by the Medical Research Council (maximal score: 150) (23), by the modified Norris limb score (maximal score: 63) and Norris bulbar score (maximal score: 39) (24), and by the ALS Functional Rating Scale (maximal score: 40) (25). The neurologist specified the precise date of appearance of first signs, the form of disease onset (bulbar or spinal), and the Ashworth spasticity score for all extremities (26). Patients self-recorded their fasciculations by using a visual analogue scale (0–100 mm). All patients were treated with a benzothiazole (50 mg riluzole twice per day) with the goal of reducing neuronal excitotoxin-related disease progression (27); the starting date of treatment was noted. No patient received any steroid drug treatment. The study ended 1 February 2000; if a patient died before this time, the date of the death was recorded.

Measurement of vital capacity

Forced vital capacity (FVC) was measured with a Hans Rudolph pneumotachograph, integrated in a body plethysmography system 1085 (CPF Medical Graphics, St Paul). Results were expressed in relation to a theoretical calculated index value.

Laboratory analysis

Serum C-reactive protein (CRP) concentrations were measured (model 911 Automatic Analyser; Hitachi, Tokyo) and complete blood cell counts were made, including a white blood cell differential. Thyroid hormone assays (Automatic Analyser; Cobas Argos, ABX, Montpellier, France) were performed on the same day as was indirect calorimetry (RIA-gnost hTSH; Cis Bio International, Gif-sur-Yvette, France).

Statistical analysis

Statistical analysis was conducted with STATVIEW 5.0 F software (Abacus Concepts Inc, Berkeley, CA). The results are given as means ± SDs. Qualitative results were compared by using a chi-square test or Fisher's exact test. Quantitative averages were compared by using the Mann-Whitney *U* test or Student's *t* test. First, statistical analysis was performed on parameters linked to mREE by simple linear regression. Similar analyses were also performed in which mREE was replaced by mREE/*Z*100 (bioimpedance at 100 kHz, in ohms) because bioimpedance at 100 kHz is considered one of the main variables explaining total body water and FFM (28). Next, an analysis was performed after normalization for FFM by using mREE adjusted for FFM (mREE/FFM), according to several recent studies of energy expenditure (29, 30) and mREE adjusted for cREE (mREE/cREE) to standardize our results with those of another rare metabolic study in ALS patients (14). We also looked for the presence of a nonlinear relation between REE, FVC, and other variables. Finally, multivariate analyses were conducted by using a multiple linear regression and integrating all the factors for which the *P* value in the simple linear regression was ≤0.25. The threshold for significance was set at 0.05 for all statistical analyses.

TABLE 1
Comparisons between patients with amyotrophic lateral sclerosis (ALS) and a healthy control group[1]

Variable	ALS patients			Control group (n = 31)
	Total (n = 62)	Men (n = 32)	Women (n = 30)	
Age (y)	63 ± 11	60 ± 10	65 ± 13	66 ± 3
Weight (kg)	64.8 ± 15.5	73.7 ± 14.1	55.3 ± 10.4	70.4 ± 11.3
BMI (kg/m^2)	24.6 ± 5.2	25.4 ± 4.4	23.7 ± 5.9	25.1 ± 2.6
Fat-free mass (kg)	46.9 ± 11.6	55.5 ± 8.7	37.7 ± 5.9	48.8 ± 9.7
Measured REE				
(kJ/d)	6527.5 ± 1430.8	7375.2 ± 1238.1	5623.4 ± 1014.9	5926.0 ± 797.1[2]
(kcal/d)	1561.6 ± 342.3	1764.4 ± 296.2	1345.3 ± 242.8	1417.7 ± 190.7[2]
RQ	0.81 ± 0.04	0.81 ± 0.04	0.81 ± 0.04	0.79 ± 0.03

[1] $\bar{x}$ ± SD. REE, resting energy expenditure; RQ, respiratory quotient (carbon dioxide production/oxygen consumption).
[2] Significantly different from total ALS patients, P = 0.03.

RESULTS

The main characteristics of the 62 subjects are presented in **Table 1**. REE was measured several times in each patient ($\bar{x}$ ± SD: n = 21.1 ± 2.7); the mean repeatability coefficient was 7.3 ± 3.2%. The mREE of the ALS patients was significantly different (10.1% greater) from that of the control group. Weight, BMI, and FFM tended to be lower in the ALS patients than in the control group, but not significantly so. In comparison with cREE values in the control group (5630.5 ± 1098.5 kJ/d, or 1347.0 ± 262.8 kcal/d), hypermetabolism was 15.9 ± 13.3% greater in the ALS patients (P < 0.0001), and 67.7% of the ALS patients had a metabolic level ≥10% of the cREE. The FVC of the ALS patients was not greatly altered from reference values, being 77.9 ± 31.4% of the theoretical value; 25.4% of the ALS patients were smokers.

Results of the neurologic, respiratory, and laboratory assessments are shown in **Table 2**. Thyroid assays showed no hyperthyroidism in any of the patients. There was no nonlinear relation between mREE, FVC, or other variables. mREE was not correlated with the intensity of spasticity as measured by the Ashworth scale (r = 0.09), the intensity of fasciculations evaluated by the visual analogue scale (r = 0.08), FVC (r = 0.14), or tobacco use (r = 0.14). Because the men had elevated CRP concentrations, their data were examined separately, even though the sample size was limited. The CRP concentration was not correlated with mREE (r = 0.03), mREE/$Z$100 (r = 0.01), mREE/FFM (r = 0.04), or mREE/cREE (r = 0.05).

A matrix of the correlation coefficients for the REE variables versus the body-composition variables and CRP, leukocyte, lymphocyte, neutrophil, and monocyte concentrations is given in **Table 3**.

Results of the multivariate analyses are given in **Table 4**. The only variable that correlated with all 4 metabolic measures (mREE, mREE/$Z$100, mREE/FFM, and mREE/cREE) was the neutrophil count. As a group, the significant factors explained 73% of the variance for the analysis with use of mREE alone and 76% with use of mREE/$Z$100, but only 20% with use of mREE/FFM and 17% with use of mREE/cREE. Although the

TABLE 2
Results of neurologic, respiratory, and laboratory assessments in patients with amyotrophic lateral sclerosis (ALS)[1]

Variable	ALS patients		
	Total (n = 62)	Men (n = 32)	Women (n = 30)
Disease duration (mo)	24.0 ± 25.6[2]	23.6 ± 23.8	24.5 ± 27.7
Duration of treatment with a benzothiazole (mo)	11.1 ± 17.3	9.3 ± 12.0	13.1 ± 21.6
Patients with bulbar-onset ALS (%)	33.9	25.0	43.3
Manual muscular testing score (23)	118.4 ± 26.7	120.0 ± 25.6	116.8 ± 28.1
Norris bulbar score (24)	29.2 ± 9.7	31.3 ± 8.3	27.1 ± 10.7
Norris limb score (24)	44.5 ± 16.3	46.0 ± 15.6	43.0 ± 17.2
ALS Functional Rating Scale (25)	29.0 ± 7.0	29.5 ± 7.2	28.5 ± 6.9
Ashworth spasticity score (26)	13.1 ± 3.1	12.9 ± 3.1	13.4 ± 3.2
Fasciculation index (mm)	35.3 ± 22.5	40.8 ± 21.6	30.1 ± 22.6
Leukocytes (× 10^6/L)[3]	6.3 ± 1.7	6.5 ± 1.7	6.1 ± 1.6
Lymphocytes (× 10^6/L)[4]	1.8 ± 0.7	1.9 ± 0.7	1.7 ± 0.6
Neutrophils (× 10^6/L)[5]	3.5 ± 1.4	4.0 ± 1.5	3.9 ± 1.3
Monocytes (× 10^6/L)[6]	0.4 ± 1.9	0.4 ± 0.2	0.4 ± 1.9
C-reactive protein (mg/L)[7]	4.9 ± 11.1	6.9 ± 13.9	2.8 ± 7.0
Forced vital capacity (% of theoretical value)	77.9 ± 31.4	74.0 ± 30.1	82.9 ± 33.0

[1] There were no significant differences between men and women.
[2] $\bar{x}$ ± SD.
[3] Normal range: 4.0–9.0 × 10^6/L.
[4] Normal range: 0.8–4.0 × 10^6/L.
[5] Normal range: 2.2–6.5 × 10^6/L.
[6] Normal range: 0.1–1.0 × 10^6/L.
[7] Normal range: <5 mg/L.

TABLE 3
Correlation coefficients for the resting energy expenditure (REE) variables versus the body-composition variables and C-reactive protein (CRP), leukocyte, lymphocyte, neutrophil, and monocyte concentrations in patients with amyotrophic lateral sclerosis (ALS)[1]

	mREE			mREE/*Z*100			mREE/FFM			mREE/cREE		
	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women
Weight	0.84	0.80	0.66	0.83	0.76	0.74	−0.27	0.02	−0.05	0.02	−0.16	0.15
BMI	0.45	0.73	0.20	0.52	0.74	0.34	−0.16	0.09	−0.20	0.09	−0.02	−0.17
FFM	0.83	0.78	0.60)	0.91	0.92	0.89	−0.46	−0.22	−0.29	0.08	−0.04	0.15
CRP	0.09	0.03	−0.31	0.11	0.01	−0.34	−0.12	0.04	−0.17	−0.06	0.05	−0.30
Leukocytes	0.34	0.44	0.24	0.34	0.49	0.05	0.19	0.02	0.44	0.32	0.21	0.42
Lymphocytes	0.29	0.34	0.08	0.36	0.46	0.02	−0.08	−0.21	0.15	0.11	0.01	0.19
Neutrophils	0.27	0.37	0.21	0.24	0.37	0.07	0.22	0.14	0.37	0.30	0.21	0.19
Monocytes	0.12	0.23	−0.13	0.15	0.24	−0.11	0.48	0.11	0.11	0.21	0.21	0.19

[1] FFM, fat-free mass; mREE, measured REE; *Z*100, bioimpedance at 100 kHz; cREE, calculated REE. For the total population, $r \geq 0.25$ ($P < 0.05$); for either men or women, $r \geq 0.35$ ($P < 0.05$).

neutrophil count was significantly correlated with all of the REE values in simple linear regression, it explained only 5% of the variance in mREE, 4% of the variance in mREE/*Z*100, 3% of the variance in mREE/FFM, and 7% of the variance in mREE/cREE. Tobacco use, spasticity score, level of fasciculations, and FVC did not correlate with the REE values in the multivariate analyses.

DISCUSSION

The finding of an mREE value that was 10.1% greater in the ALS patients than in the control group confirmed the existence of hypermetabolism in ALS patients. This finding was also confirmed by a comparison with cREE. This recurring finding of hypermetabolism is surprising because denervation and a rapid reduction in physical activities usually cause muscle atrophy in ALS patients, which is consistent with a reduction in FFM (14, 31, 32). Such a reduction in FFM was shown by several other researchers, who used various techniques to analyze body composition, eg, anthropometric measures, dual-energy X-ray absorptiometry, and comparisons between study populations (16, 31–33). It is known that REE, which represents ≈60% of total daily energy expenditure, is positively correlated with FFM, is inversely correlated with age, and is greater in men than in women (34). Thus, considering the slightly lower weights and FFM values in our ALS patients than in the control group, one would expect overall hypometabolism or normometabolism in ALS patients. Consequently, the finding of an inverse result suggests the need to look for an unexpected factor that is correlated with REE.

REE is the energy required for the maintenance of normal bodily functions and for homeostasis. REE includes, in particular, the energy necessary to maintain cardiorespiratory, cerebral, and nervous system functions and the energy needed for multiple biochemical reactions required for bodily homeostasis. In contrast, REE does not include the energy expenditure associated with physical activity nor the energy expenditure resulting from absorption, metabolism, and storage of food intake. Hyperthyroidism, infection, and inflammation can cause an increase in REE; however, these conditions were not a factor in our study because none of the hypermetabolic patients was hyperthyroid and patients with clinical infection were excluded.

Although the average CRP concentration of the total ALS population in the present study was normal, the average concentration in men was slightly outside the normal range but was not correlated significantly with any of the REE variables. It has been known for many years that thyroid disorders are rarely seen in ALS patients (35, 36). Thus, another pathophysiologic mechanism to explain the hypermetabolism observed in ALS patients must be envisioned, such as the "respiratory hypothesis" proposed in 1996 by Kasarskis et al (14). These authors used indirect calorimetry to determine REE in 16 ALS patients who were not receiving any ventilatory assistance and who had a mean BMI of 21.7–23.0. They noted the appearance of a state of hypermetabolism in the end-stage of ALS (mREE/cREE increased from 0.83 at the first calorimetric assessment to 1.23 at the last assessment before death). In contrast, FFM and BMI decreased in the same period. Nevertheless, mREE was not studied in relation to FFM. The authors suggested that respiratory muscular

TABLE 4
Variables significantly associated with mREE, mREE/*Z*100, mREE/FFM, or mREE/cREE in a multivariate analysis[1]

	P value in multivariate analysis with mREE	*P* value in multivariate analysis with mREE/*Z*100	*P* value in multivariate analysis with mREE/FFM	*P* value in multivariate analysis with mREE/cREE
Age (y)	0.03 (−)	—	—	—
Sex (men = 1)	—	—	0.0001 (−)	—
FFM (kg)	0.0001 (+)	—	—	—
Manual muscular testing score (23)	—	—	—	<0.02 (+)
Weight (kg)	—	0.0001 (+)	—	—
Norris limb score (24)	<0.001 (+)	—	—	—
Neutrophils	0.006 (+)	<0.003 (+)	0.05 (+)	0.02 (+)

[1] (+), positive association with increase; (−), inverse association with increase; REE, resting energy expenditure; mREE, measured REE; *Z*100, bioimpedance at 100 kHz; cREE, calculated REE; FFM, fat-free mass.

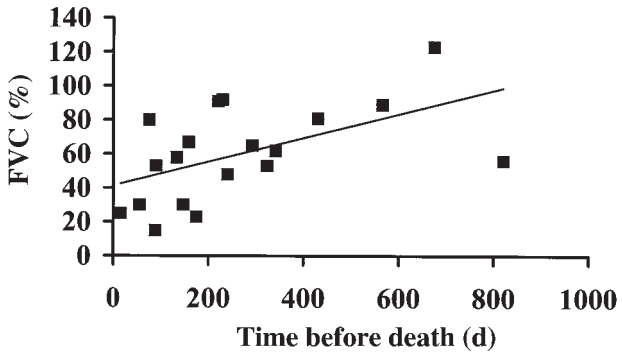

FIGURE 1. Evolution of forced vital capacity (FVC) in patients with amyotrophic lateral sclerosis ($n = 19$) as they approached death. $r = 0.54$, $P = 0.02$.

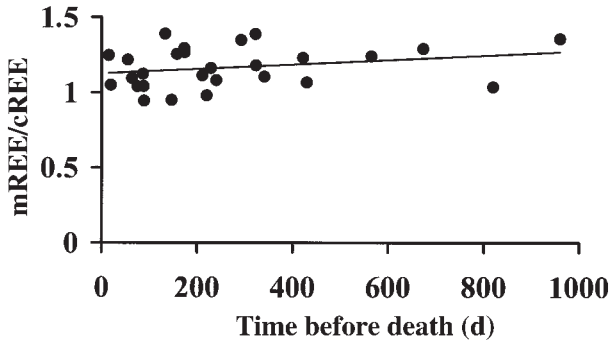

FIGURE 2. Changes in measured resting energy expenditure (mREE) adjusted for calculated REE (cREE) in patients with amyotrophic lateral sclerosis ($n = 27$) as they approached death. $r = 0.26$, $P = 0.18$.

expenditures increased in their patients as the patients attempted to remain alive at the end-stage of the disease. The authors also noted the different disease-progression patterns of men and women as evidenced by body-composition measures and respiratory quotients. They suggested that abnormalities of the metabolic or endocrine system, or both, accounted for the differences in disease progression observed.

The results of the much earlier study by Shimizu et al (37) indicated a major role of respiratory function on energy expenditure. In that study, the total energy expenditure of 11 ALS patients was studied by 24-h indirect calorimetry. The resting energy expenditure in these patients was very low: 11.3–26.8% less than the value obtained by using the Harris-Benedict equation (20). This marked hypometabolism may have resulted because of all the patients in this study were on ventilators; thus, the energy expenditure required to maintain respiration was very low or nonexistent. However, the poor nutritional state of the patients may also have been the reason for the observed hypometabolism. The mean BMI of these patients was 15.3 ± 2.5, the reasons for which was unspecified.

In our patient population, we explored the respiratory hypothesis for hypermetabolism by looking for an association between the principal respiratory criteria often used in the follow-up of ALS patients: FVC and mREE. FVC was not associated with mREE in any of the analytic models used, suggesting that the respiratory hypothesis was not satisfactory. Moreover, although FVC decreased significantly as the ALS patients approached death (**Figure 1**), as was also noted by Kasarskis et al (14), mREE/cREE and mREE appeared to remain stable (**Figure 2**).

Another plausible contributor to hypermetabolism is tobacco smoking because it can induce a 6–10% increase in REE by heightened sympathoadrenal activation and via direct thermogenic effects of nicotine (38, 39). Changes in the mitochondrial respiratory chain complex IV in human lymphocytes was also shown to be associated with tobacco use (40). Yet, although ≈25% of the ALS patients in the present study were smokers, tobacco smoking did not have a significant effect on REE and did not explain the observed hypermetabolism.

Fasciculations, spasticity, or both have also been hypothesized to play a role in hypermetabolism because they can increase the basic muscular tone, which contributes to the REE (41). Yet, we found no correlation between fasciculation or spasticity scores and REE; hence, these alterations in muscle tone did not appear to explain the hypermetabolism observed in our ALS patients. Moreover, no published data suggest a possible role of riluzole in modifying REE.

Metabolic changes in leukocytes can affect cytokine secretion, possibly thereby altering energy expenditure. The hypothesis that cytokines play a role in the genesis of neuronal damage in ALS was raised by several authors (42, 43). Cytokine production by astrocytes, microglial cells, or both has been suggested to enhance the production of free radicals, which can induce adjacent neuronal damage; peroxynitrite, in particular, has been suspect (43–47). Such toxic injury to neurons may ultimately lead to neuronal death (47), possibly via the intermediary step in which certain components of the mitochondrial respiratory chain are inhibited or via an increase in mitrochondrial leakage in both the sporadic and familial ALS forms, although likely to differing degrees (43, 48, 49). Such mitochondrial derangements would cause excessive heat production, accounting for the appearance of hypermetabolism and potentially causing an energy deficit, which can lead to cellular degradation (49). In fact, this pathophysiologic mechanism has not only been suspected in ALS, but also in the development of other neurodegenerative diseases (eg, Alzheimer disease and Parkinson disease) and in tissue injury from strokes (41, 43, 44, 50). However, hypermetabolism is not necessarily found in patients with these other diseases. A recent study showed a state of hypometabolism in patients with Alzheimer disease relative to a healthy control population (51). Some authors reported the same finding, ie, hypometabolism, in Parkinson disease (50) whereas others reported hypermetabolism in Parkinson disease (41).

There exists, in the circulating lymphocytes of sporadic ALS patients, elevated cytosol calcium concentrations and a reduced response to decouplants of oxidative phosphorylation reactions, suggesting a dysfunction of mitochondrial and calcium metabolism (52). We found an elevated neutrophil count in the circulating leukocytes of the ALS patients. Furthermore, the neutrophil count was significantly associated with the various REE measurements, although the reasons for this are not fully known. Considering the small percentage of variance explained by the aggregate of factors significantly associated with an elevated REE and the absence of a significant relation between CRP concentrations and REE values, it is likely that factors other than those investigated in our study play a role in hypermetabolism in ALS patients. It would be of interest to determine what the possible metabolic mitochondrial derangements are within the subpopulation of hypermetabolic patients. Additionally, further study of sympathetic system

activation might yield additional clues to the autonomic dysregulation that is hypothesized to exist in ALS (53, 54).

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