ORIGINAL ARTICLE

Hypermetabolism is a deleterious prognostic factor in patients with amyotrophic lateral sclerosis

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Background and purpose: The aim of this study was to investigate patients with amyotrophic lateral sclerosis in order to determine their nutritional, neurological and respiratory parameters, and survival according to metabolic level.

Methods: Nutritional assessment included resting energy expenditure (REE) measured by indirect calorimetry [hypermetabolism if REE variation (ΔREE) > 10%] and fat mass (FM) using impedancemetry. Neurological assessment included the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised score. Survival analysis used the Kaplan–Meier method and multivariate Cox model.

Results: A total of 315 patients were analysed. Median age at diagnosis was 65.9 years and 55.2% of patients were hypermetabolic. With regard to the metabolic level (ΔREE: < 10%, 10–20% and >20%), patients with ΔREE > 20% initially had a lower FM (29.7% vs. 32.1% in those with ΔREE ≤10%; $P = 0.0054$). During follow-up, the median slope of Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised tended to worsen more in patients with ΔREE > 20% (−1.4 vs. −1.0 points/month in those with ΔREE ≤10%; $P = 0.07$). Overall median survival since diagnosis was 18.4 months. ΔREE > 20% tended to increase the risk of dying compared with ΔREE ≤10% (hazard ratio, 1.33; $P = 0.055$). In multivariate analysis, an increased REE:FM ratio was independently associated with death (hazard ratio, 1.005; $P = 0.001$).

Conclusions: Hypermetabolism is present in more than half of patients with amyotrophic lateral sclerosis. It modifies the body composition at diagnosis, and patients with hypermetabolism >20% have a worse prognosis than those without hypermetabolism.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder. ALS incidence is stable among the different Western populations at 2/100 000 person years [1,2]. Its prognosis is severe with a median survival of 25–30 months after diagnosis in Europe [3,4]. Malnutrition is a risk in the short and medium term, and may be present at diagnosis [5,6]. Alteration of nutritional status is multifactorial but two main causes are involved: decreased food intake and increased resting energy expenditure (REE) [4,6,7]. Previous studies reported hypermetabolism in 50–60% of patients, characterized by an increase in REE value of between 10% and 20% [7,8]. If REE increase is not compensated for by an adequate diet, the consequence is weight loss associated with feeding difficulties. The impact of hypermetabolism on survival remains

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controversial. Bouteloup *et al*. [8] found no association with survival in a small population of 61 patients.

Analysis on a larger cohort is needed to study the prognostic role of hypermetabolism, which could be systematically sought by nutritional evaluation of patients with ALS. The secondary objective was to analyse the clinical parameters associated with hypermetabolic status.

Methods

The diagnosis of ALS was reached according to Airlie House criteria [9]. Patients were prospectively followed in the ALS referral centre in Limoges from time of diagnosis to death. The presence of cognitive or behavioural features was not considered to be an exclusion criterion. All patients were treated with riluzole. Clinical assessments were performed every 3 months. Clinical data of patients with ALS were retrospectively extracted from the national CleanWEB^{TM} database with authorization by the Commission Nationale de l'Informatique et des Libertés. All of the patients gave their informed consent for data collection.

Date of diagnosis, indirect calorimetry (IC), gastrostomy placement, non-invasive ventilation placement, tracheostomy and death confirmed by a death certificate were recorded.

Measured REE (mREE) (in kcal/24 h) by IC was performed on the Quark RMR® with canopy (Cosmed, Rome, Italy) after a calibration (±0.02% on measures of expired volumes of CO_2 and inspired volumes of O_2) [10]. IC was performed once during the first 12 months after diagnosis, in the morning after 12 h of fasting, in a supine position and at rest. The patient was not physically active before the IC, did not sleep during the examination and did not hyperventilate. The respiratory quotient should have been between 0.7 and 0.87 [10]. REE was also calculated (cREE) (in kcal/24 h) according to the predictive formulas of Harris and Benedict [11]. REE variation (ΔREE) (in %) was calculated according to the formula: (mREE (kcal/24 h) – cREE (kcal/24 h))/cREE (kcal/24 h) * 100. Hypermetabolism was defined as a ΔREE > 10% of the calculated value [7]. IC should be performed during the evaluation of other nutritional parameters or within a maximum of 1.5 months following this evaluation. Patients were weighed in underwear using a SECA® electronic balance (Vogel & Halke, Hamburg, Germany) in an upright position or on a SECA® weighing chair. The usual weight 6 months before onset of symptoms was collected allowing calculation of the percentage of initial weight loss relative to the usual weight. Height (in m) was measured using a SECA® gauge in an upright position. Body mass index (BMI) (kg/m^2) was calculated. The triceps skin fold was measured on each side with a Harpenden caliper (Baty International, Burgess Hill, UK) according to the usual modalities [12]. Free fat mass (FFM) (in kg and %) and fat mass (FM) (in kg and %) were calculated with the validated formula for patients with ALS with body impedance at 50 kHz using an Analycor® device (Eugédia, Chambly, France) in a supine position after 5 min of rest [13]. The impedancemetry also allowed for measurement of phase angle (in °) [14]. Malnutrition was defined according to the French criteria: BMI < 18.5 (<70 years) and BMI < 21.0 (≥70 years) [15]. Normal status was defined as a BMI between 18.5 and 24.9 (<70 years), and between 21.0 and 26.9 (≥70 years). Overweight was defined as a BMI between 25.0 and 29.9 (<70 years), and between 27.0 and 29.9 (≥70 years). Obesity was defined as a BMI ≥ 30.

Neurological assessment recorded ALS phenotypes [bulbar, spinal, spinal cervical, spinal lumbar, flail arm, flail leg, respiratory, drooping head, ALS/frontotemporal dementia (FTD)] [16]. The presence of a familial background of ALS (FALS) and/or FTD prompted genetic testing. Functional decline was recorded on the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) (on 40 points before 2009) and Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) (on 48 points after 2009). To homogenize the results, ALSFRS was converted into a score on 48 points [4]. Manual muscular testing (on 150 points) was also recorded [17].

Respiratory assessment included measurements of the slow vital capacity (in % of the theoretical value), forced vital capacity, maximal inspired and expired pressures (expressed in % of the theoretical value), and SNIFF test (in % of the theoretical value) using a Hans Rudolph® pneumotachograph, integrated into a body plethysmography system 1085 (CPF Medical Graphics, St Paul, MN, USA).

Statistical analysis was performed using SAS® software (SAS Institute, Cary, NC, USA). Quantitative variables were expressed as the median (interquartile range). Qualitative variables were expressed as number and percentage. Quantitative variables were compared using non-parametric Mann–Whitney or Kruskal–Wallis tests if there were more than two groups. In case of overall statistical significance of a Kruskal–Wallis test, *post-hoc* analysis of 2 by 2 differences was performed using a Mann–Whitney test. Level of significance for *post-hoc* tests was adapted according to Bonferroni (0.05/3 = 0.017) to avoid alpha risk inflation. Qualitative variables were compared using chi

square or Fisher tests. The comparative analysis was carried out according to ΔREE, using three classes; ΔREE ≤ 10%, 10–20% and >20%. A test for trend was performed while comparing baseline or evolution during follow-up by categories of ΔREE. This was performed using a Cochran Armitage test for qualitative variable or linear trend within ANOVA analysis of ranks of the quantitative variables. Correlation between ΔREE (used as quantitative variable) and other quantitative variables was realized using a Spearman test. For the survival analysis the event was the date of death or tracheostomy. Univariate survival analysis was performed using the Kaplan–Meier method and log-rank test. Multivariate survival analysis was performed with the Cox model. Association between REE and survival was systematically adjusted on potential confusion factors or well-known prognostic factors for survival: sex, age at diagnosis, bulbar onset, ALSFRS-R slope at diagnosis, gastrostomy and non-invasive ventilation placement (time-dependent covariates for the last two factors). The threshold of significance for all statistical analyses was $P < 0.05$. We complied with the STROBE statement [18].

Results

From November 1996 to November 2014, 405 patients with ALS had an IC and 315 patients were included (Fig. 1). Excluded patients differed from included patients in that they displayed a significantly better survival [34.4 (24.1–47.2) vs. 18.4 (11.2–30.9) months; $P < 0.0001$]. However, other criteria and the percentage of hypermetabolism were not significantly different between excluded and included patients ($P = 0.55$).

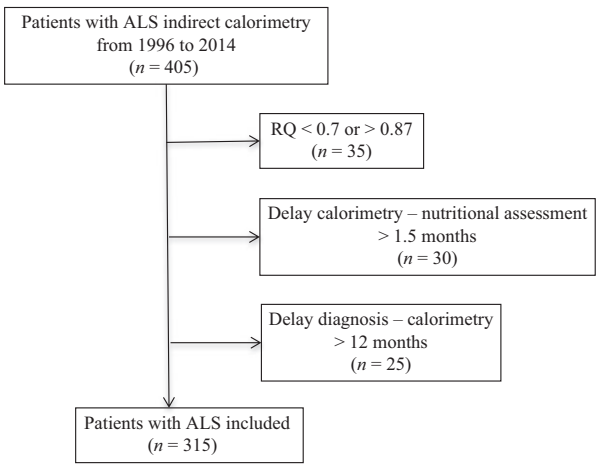

Figure 1 Flowchart of patients with amyotrophic lateral sclerosis (ALS) included in the study. RQ, respiratory quotient.

Median age at diagnosis of the 315 patients was 65.9 (56.5–73.7) years with a sex ratio of 1.0. Hypermetabolism was found in 55.2%. The median ΔREE was 18.3% (13.8–25.9%) in hypermetabolic patients (Table 1). The first nutritional assessment was performed within a median of 4.3 (2.2–6.6) months after diagnosis.

Initial weight loss tended to be different according to ΔREE ranges (≤10%, 10–20% and >20%): −4.9 (−10.9 to −0.1), −4.8 (−7.1 to 0.8) and −5.4 (−12.2 to −2.3) kg, respectively ($P = 0.06$) (Table 2). Body composition was also different with a significantly lower percentage of FM in patients with ΔREE > 20% vs. ≤10% [29.7% (20.4–34.6%) vs. 32.1% (26.1–40.7%); $P = 0.005$]. No difference was found in the three metabolic groups according to the

Table 1 Nutritional, neurological and respiratory characteristics of patients with amyotrophic lateral sclerosis (ALS) at the first assessment

Criterion		*n*
Age at diagnosis (years)	65.9 (56.5–73.7)	315
Sex ratio (M:F)	161:154	315
Clinical phenotype		
Bulbar form	124 (39.4)	315
Spinal cervical form	79 (25.1)	315
Spinal lumbar form	84 (26.6)	315
ALS/FTD form	24 (7.6)	315
Proximal impairment of limbs	51 (17.8)	287
Hypermetabolic patients	174 (55.2)	315
mREE (kcal/24 h)	1503 (1290–1698)	315
ΔREE (%)	11.8 (3.7–19.8)	315
Usual weight (kg)	70.0 (61.0–79.0)	282
Usual BMI (kg/m^2)	25.9 (23.6–29.3)	282
Weight (kg)	65.0 (57.3–74.7)	315
BMI (kg/m^2)	24.2 (22.0–27.6)	315
Weight loss (%)	−4.9 (−10.5 to −0.3)	282
TSF (mm)	12.9 (9.5–18.3)	306
FFM (kg)	44.4 (36.9–51.9)	287
FFM (%)	68.6 (60.4–75.4)	287
FM (kg)	20.7 (15.2–25.4)	287
FM (%)	31.4 (24.6–39.6)	287
PA (°)	3.0 (2.4–3.7)	299
ALSFRS-R (points)	40 (35–43)	291
MMT (points)	136 (121–144)	306
SVC (%)	93.0 (72.0–110.0)	234
FVC (%)	90.0 (69.0–106.0)	239
IP_{max} (%)	56.0 (39.0–81.0)	199
EP_{max} (%)	55.5 (39.0–77.0)	202
SNIFF (%)	50.0 (35.0–70.0)	209

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BMI, body mass index; EP_{max}, maximal expired pressure; F, female; FFM, free fat mass; FM, fat mass; FTD, frontotemporal dementia; FVC, forced vital capacity; IP_{max}, maximal inspired pressure; M, male; MMT, manual muscular testing; mREE, measured resting energy expenditure; PA, phase angle; ΔREE, resting energy expenditure variation; SVC, slow vital capacity; TSF, triceps skin fold. Data are given as median (interquartile range) or *n* (%).

Table 2 Nutritional, neurological and respiratory characteristics of patients with and without hypermetabolism at the first assessment

	ΔREE ≤ 10% (n = 141)	ΔREE 10–20% (n = 101)	ΔREE > 20% (n = 73)	P for differences between groups	P for linear trend[c]
Age (years)	66.8 (54.4–74.2)	64.4 (56.4–71.6)	66.9 (60.3–71.8)	0.50	0.30
Sex (% male)	62 (44.0)	50 (49.5)	49 (67.1)[b]	**0.005**	**0.002**
Bulbar form	59 (41.8)	34 (33.7)	31 (42.5)	0.38	0.97
Spinal cervical form	35 (24.8)	23 (22.8)	21 (28.8)	0.63	0.65
Spinal lumbar form	31 (22.0)	37 (36.6)	16 (21.9)	**0.02**	0.65
ALS/FTD form	16 (11.3)	3 (3.0)	5 (6.8)	0.051	0.12
Proximal impairment of limbs	20 (15.7)	24 (25.8)	7 (10.4)	**0.03**	0.65
mREE (kcal/24 h)	1339.0 (1155.0–1540.0)	1560.0 (1373.0–1734.0)	1666.0 (1520.0–1840.0)	**< 0.0001**	**< 0.0001**
ΔREE (%)	2.3 (−3.1 to 6.1)	14.6 (12.6–16.8)	26.9 (24.1–30.9)	**< 0.0001**	**< 0.0001**
REE/weight (kcal/kg/24 h)	24.0 (23.0–26.0)	23.2 (22.3–24.9)	26.4 (24.6–27.9)	**< 0.0001**	**< 0.0001**
REE/FFM (kcal/kg/24 h)	36.0 (32.0–39.0)	35.0 (31.5–38.4)	37.4 (33.7–40.4)	**< 0.0001**	**< 0.0001**
REE/FM (kcal/kg/24 h)	79.0 (63.0–108.3)	72.2 (59.1–99.8)	87.1 (72.9–132.9)	**< 0.0001**	**< 0.0001**
Usual weight (kg)	72.0 (60.0–80.0)	70.0 (61.0–78.0)	70.0 (63.0–76.0)	0.84	0.59
Usual BMI (kg/m^2)	26.7 (23.6–29.8)	25.9 (23.8–29.1)	25.6 (22.9–28.5)	0.51	0.19
Weight (kg)	65.4 (56.5–75.0)	66.2 (58.3–75.2)	63.8 (56.4–73.6)	0.61	0.47
BMI (kg/m^2)	24.4 (21.8–28.0)	24.4 (22.5–27.6)	24.0 (21.8–25.9)	0.45	0.17
Weight loss (%)	−4.9 (−10.9 to −0.1)	−4.8 (−7.1 to 0.8)	−5.4 (−12.2 to −2.3)	0.062	0.059
TSF (mm)	14.4 (10.3–19.0)	12.5 (9.5–19.2)	11.4 (8.6–16.0)[b]	**0.03**	**0.01**
FFM (kg)	42.5 (36.0–51.5)	45.2 36.7–52.8)	45.2 (40.0–51.6)	0.14	0.09
FFM (%)	67.9 (59.3–73.9)	67.5 (60.4–75.3)	70.3 (65.4–79.6)[b]	**0.01**	**0.002**
FM (kg)	20.9 (15.5–26.7)	21.0 (16.0–25.3)	18.8 (13.2–24.1)	0.10	**0.02**
FM (%)	32.1 (26.1–40.7)	32.5 (24.7–39.6)	29.7 (20.4–34.6)[b]	**0.01**	**0.002**
PA (°)	3.0 (2.3–3.7)	3.0 (2.5–3.7)	3.1 (2.5–3.4)	0.39	0.87
ALSFRS-R (points)	38.0 (32.0–42.0)	41.0 (36.0–43.0)[a]	40.0 (35.0–43.0)	**0.01**	0.23
ALSFRS-R slope (points/month)	−1.1 (−2.0 to −0.7)	−1.0 (−2.0 to −0.5)	−1.2 (−2.4 to −0.7)	0.34	0.67
MMT (points)	133.0 (116.0–143.0)	137.0 (126.0–144.0)	136.5 (120.0–146.0)	0.40	0.56
SVC (%)	92.0 (75.0–108.0)	101.0 (71.0–113.0)	87.0 (70.0–107.0)	0.40	0.33
FVC (%)	89.0 (73.0–103.0)	98.5 (71.0–114.0)	84.0 (66.0–102.5)	0.21	0.47
IP_{max} (%)	55.0 (42.0–81.0)	67.0 (45.0–84.0)	47.5 (32.0–75.0)	0.10	0.16
EP_{max} (%)	62.0 (35.0–82.5)	57.5 (40.5–79.0)	49.0 (40.0–72.0)	0.42	0.43
SNIFF (%)	54.0 (41.0–71.0)	50.0 (35.0–71.0)	36.0 (29.0–66.0)	0.07	**0.03**

ALS, amyotrophic lateral sclerosis; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BMI, body mass index; EP_{max}, maximal expired pressure; FFM, free fat mass; FM, fat mass; FTD, frontotemporal dementia; FVC, forced vital capacity; IP_{max}, maximal inspired pressure; MMT, manual muscular testing; mREE, measured resting energy expenditure; PA, phase angle; ΔREE, resting energy expenditure variation; REE, resting energy expenditure; SVC, slow vital capacity; TSF, triceps skin fold. [a]Comparison of patients with REE variation ≤10% vs. 10–20% ($P < 0.017$). [b]Comparison of patients with REE variation ≤10% vs. >20% ($P < 0.017$). [c]Linear trend using Cochran Armitage test for qualitative variable or linear trend within ANOVA analysis of ranks of the quantitative variables.Data are given as median (interquartile range) or n (%); values in bold indicate $P < 0.05$.

ALS form and degree of upper motor neuron dysfunction. Hypermetabolism was found in 54.5% of FALS (n = 33), with no difference in percentage according to ΔREE ranges. Of 26 patients with FALS who underwent genetic testing, 11 had a C9orf72 mutation with no difference in frequency according to ΔREE. Other mutations were reported as follows: SOD1, 13.3%; exon 3 FUS/TLR, 13.3%; SCA2, 6.7%; TARDBP, 6.7%. At the time of IC, only SNIFF tended to decrease when ΔREE increased [54.0% (<10%) vs. 50.0% (10–20%) vs. 36.0% (>20%); P = 0.07)]. The correlations between ΔREE and the quantitative baseline variables are presented in Table S1. We found significant correlations between ΔREE and ALSFRS-R (ρ, 0.12; P = 0.04) and between ΔREE and SNIFF (ρ, −0.19; P = 0.005). We found a significant difference in ΔREE between the sexes for qualitative variables [male, 13.2% (5.3–23.3%); female, 8.9% (1.5–16.5%); P = 0.0007].

After 10.2 (5.8–19.5) months, the nutritional parameters did not differ according to the metabolic level (Table 3), contrasting with the ALSFRS-R slope, which increased with the metabolic level: −1.0 (<10%), −1.2 (10–20%) and −1.4 (>20%) points/month (P = 0.07). The metabolic level did not modify the delay in gastrostomy or non-invasive ventilation

Table 3 Evolution of nutritional, neurological and respiratory characteristics of patients with and without hypermetabolism during follow-up

	ΔREE ≤ 10% (n = 141)	ΔREE 10–20% (n = 101)	ΔREE > 20% (n = 73)	P for differences between groups	P for linear trend[b]
Weight (%)	−2.1 (−9.4 to 4.1)	−1.5 (−5.6 to 2.7)	−2.3 (−5.8 to 1.5)	0.74	0.32
BMI (kg/m^2)	−0.6 (−2.5 to 1.0)	−0.5 (−2.3 to 1.1)	−0.78 (−2.5 to 0.6)	0.78	0.45
FFM (kg)	−17.0 (−21.3 to −12.6)	−16.7 (−23.2 to −13.7)	−19.0 (−21.7 to −14.7)	0.59	0.95
FFM (%)	−38.4 (−41.9 to −33.0)	−40.7 (−44.0 to −35.7)	−40.1 (−42.6 to −36.5)	0.43	0.21
FM (kg)	14.1 (11.7–19.3)	16.8 (11.7–21.6)	16.5 (13.6–20.1)	0.75	0.45
FM (%)	69.3 (56.1–110.2)	77.3 (43.6–116.5)	86.0 (57.8–153.7)	0.37	0.99
PA (°)	−1.0 (−1.3 to −0.4)	−0.9 (−1.7 to −0.2)	−0.7 (−1.2 to −0.2)	0.60	0.28
ALSFRS-R slope (points/month)	−1.0 (−1.6 to −0.5)	−1.2 (−2.0 to −0.7)	−1.4 (−2.1 to −0.8)	0.07	0.07
MMT (points)	−39.0 (−55.0 to −22.0)	−33.0 (−56.0 to −17.0)	−35.5 (−52.0 to −15.0)	0.62	0.67
SVC (%)	−30.0 (−49.0 to −12.0)	−42.0 (−59.0 to −17.0)	−28.5 (−47.0 to −12.0)	0.06	0.66
FVC (%)	−28.0 (−47.0 to −12.0)	−42.0 (−65.0 to −16.0)[a]	−29.5 (−48.0 to −12.0)	**0.01**	0.84
IP_{max} (%)	−15.0 (−26.0 to −2.0)	−24.0 (−49.0 to −9.0)	−17.0 (−37.0 to −6.5)	0.16	0.40
EP_{max} (%)	−19.0 (−40.0 to −5.0)	−26.0 (−56.0 to −13.0)	−20.5 (−31.5 to −11.0)	0.17	0.72
SNIFF (%)	−19.0 (−31.0 to −5.0)	−24.5 (−41.0 to −9.0)	−14.0 (−38.0 to −6.0)	0.26	0.86

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BMI, body mass index; EP_{max}, maximal expired pressure; FFM, free fat mass; FM, fat mass; FVC, forced vital capacity; IP_{max}, maximal inspired pressure; MMT, manual muscular testing; PA, phase angle; ΔREE, resting energy expenditure variation; SVC, slow vital capacity. [a]Comparison of patients with REE variation ≤10% vs. 10–20% ($P < 0.017$). [b]Linear trend within ANOVA analysis of ranks of the quantitative variables. Data are given as median (interquartile range); value in bold indicates $P < 0.05$.

placement. The correlations between ΔREE and the quantitative evolution variables during follow-up are presented in Table S2. The only significant correlation was between ΔREE and ALSFRS-R slope (ρ, −0.16; $P = 0.02$).

In univariate analysis according to the metabolic level, patients with ΔREE > 20% tended to be at increased risk of death compared with those with ΔREE ≤ 10% (hazard ratio, 1.33; 95% confidence interval, 0.99–1.79; $P = 0.055$) (Fig. 2a). Inversely, patients with mREE >1700 kcal/24 h had a decreased risk of dying of 48% compared with those with mREE ≤ 1300 kcal/24 h (hazard ratio, 0.52; 95% confidence interval, 0.38–0.73; $P = 0.0001$) (Fig. 2b). This effect on survival disappeared after normalization of mREE for FFM. The results of the univariate and multivariate survival analyses are presented in Table 4. After adjustment, these criteria were not significantly associated with survival in multivariate analysis. However, an increased mREE:FM ratio was a risk factor for death (hazard ratio, 1.005; 95% confidence interval, 1.002–1.009; $P = 0.001$).

Discussion

This study found hypermetabolism in a large cohort of 315 patients with ALS. Demographic characteristics (age at diagnosis, sex ratio) are similar to those of patients with ALS included in the FRALim registry [4]. The mean ΔREE of +20.6% is in agreement with the literature [7,8]. Patients with ΔREE >20% were more often men (67.1%) as previously reported by Desport *et al*. [7]. This increase of ΔREE may be related to FFM cellular dysfunction [19]. Hypermetabolism also occurs sporadically in patients with FALS, with a similar frequency. C9orf72 and SOD1 mutations account for 65% of FALS in France. The C9orf72 mutation (n = 11) does not modify the frequency of hypermetabolism. It would be interesting to analyze the metabolic level in pre-symptomatic C9orf72 and SOD1 cases to determine when patients with FALS become hypermetabolic.

The cause of hypermetabolism is still unknown and may involve several mechanisms [19–22]. Cortical hyperexcitability could be related to this metabolic dysfunction. This hyperexcitability could increase glucose metabolism. Indeed, an increase of metabolism of glucose, which is the main energy substrate in neurons, was found with ^{18}fluorodeoxyglucose–positron emission tomography in brains of patients with ALS [23,24]. This increase of brain glucose consumption could lead to an increase of metabolic rate in these patients. However, no link has yet been found between hypermetabolism in IC and brain hypermetabolism. A combination of ^{18}fluorodeoxyglucose–positron emission tomography brain investigation, cortical hyperexcitability analysis and REE measurement in IC seem necessary in future study. Regarding patient progression, hypermetabolic patients tend to alter their functional status more rapidly, with a steeper ALSFRS-R slope when the metabolic level increased. However, FFM, which reflects muscle mass of these patients, was not significantly different in the three groups. This ALSFRS-R alteration could be related to cortical

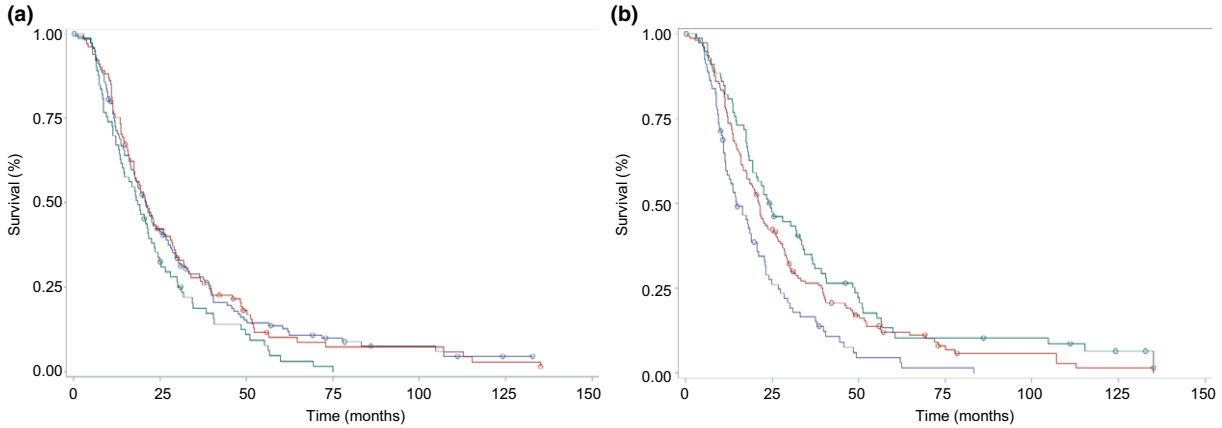

Figure 2 Survival of patients according to the level of energy expenditure in Kaplan–Meier model. (a) Blue, patients with resting energy expenditure variation (ΔREE) ≤ 10%; red, patients with ΔREE 10–20%; green, patients with ΔREE > 20%; ○, censored patients. (b) Blue, patients with measured resting energy expenditure (mREE) ≤ 1300 kcal/24 h; red, patients with mREE 1300–1700 kcal/24 h; green, patients with mREE > 1700 kcal/24 h; ○, censored patients.

Table 4 Factors associated with survival in univariate and multivariate Cox analyzes

	Survival univariate analysis				Survival multivariate analysis adjusted on model 1[a]			
Variable	HR	95% CI	*P*	*n*	HR	95% CI	*P*	*n*
Hypermetabolism (yes)	1.12	0.89–1.42	0.35	315	1.12	0.87–1.43	0.38	290
					1.07[b]	0.82–1.38	0.62	
					1.08[c]	0.83–1.40	0.57	
ΔREE (%)			0.11	315				
≤10	1							
10–20	0.99	0.76–1.31	0.99					
>20	1.33	0.99–1.79	0.055					
REE (+200 kcal increment)	0.86	0.79–0.94	**0.0005**	315				
REE (kcal/24 h)			**0.0004**	315				
≤1300	1							
1300–1700	0.64	0.49–0.85	**0.002**					
>1700	0.52	0.38–0.73	**0.0001**					
REE/FFM (kcal/kg/24 h, continuous)	0.98	0.96–1.00	0.09	287				
REE/FM (kcal/kg/24 h, continuous)	1.01	0.98–1.04	0.54	287	1.005	1.002–1.009	**0.001**	267
FFM (kg, continuous)	0.99	0.98–0.99	**0.04**	287				
FM (kg, continuous)	0.99	0.97–0.99	**0.048**	287	0.98	0.96–0.99	**0.03**	267
PA (°, continuous)	0.73	0.63–0.83	**< 0.0001**	299	0.84	0.71–1.001	0.051	274

CI, confidence interval; FFM, free fat mass; FM, fat mass; HR, hazard ratio; PA, phase angle; REE, resting energy expenditure; ΔREE, resting energy expenditure variation. [a]Covariable to adjust interest variable in multivariate analysis (model 1): sex, age at diagnosis, bulbar onset, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised slope at diagnosis, gastrostomy placement, non-invasive ventilation placement. [b]Model 1+ FM (kg). [c]Model 1+ FFM (kg); values in bold indicate $P < 0.05$.

hyperexcitability, which could lead to this hypermetabolism. Indeed, higher cortical hyperexcitability is an independent risk factor for death as ALSFRS-R evolution [25]. These two criteria could therefore be related. It is well known that REE is related to FFM. This study demonstrated that patients with a ΔREE > 20% (23.2%, $n = 73$) lost more weight at diagnosis with a modification in their body composition with a lower FM. Moreover, patients with hypermetabolism >20% of the theoretical value tend to be at a risk of death that is increased by 33% ($P = 0.055$). In addition, mREE over 1700 kcal/24 h is associated with a risk of death that is decreased by 48% ($P < 0.0001$). A recent study found a positive correlation between total energy expenditure and ALSFRS-R and forced vital capacity in 25 patients with ALS [26]. REE is strongly linked to FFM, which could suggest that patients with higher FFM have better survival. We find no protective effect after standardization of REE on the FFM. In contrast, when the ratio REE:FM increases the risk of death

also increases and, moreover, when FM decreases the REE:FM ratio increases, which would thus be an effect of FM variation on survival. Indeed, we have already described the protective effect on survival of a higher FM in patients with ALS [6]. FM therefore seems to be an important determinant of the evolution of this disease. A recent study found, in a murine model, that human stem cell injection of adipose tissue delayed the onset of the disease and improved survival with a neuroprotective effect by decreasing apoptosis and mitochondrial dysfunction [27].

Previous work showed that hypermetabolic patients increased their protein-energy intakes but lost no more weight initially than normometabolic patients [8]. These patients seem to spontaneously increase their nutritional intakes to limit the maximum weight loss. Huisman *et al*. found increased energy intakes in pre-symptomatic patients with ALS compared with controls [28]. Changes in the pathways of food intake could therefore be considered in these patients. A recent study found hypothalamic changes in the arcuate nucleus (centre of food intake regulation) in different murine models of ALS (SOD1, TDP-43 and FUS) [21]. Alteration of the anorectic pathway could be related to a decrease in the number of pro-opiomelanocortin neurons and pro-opiomelanocortin expression. Conversely, the orexigenic pathway is marked by an increased density of agouti-related peptide neurons and increased agouti-related peptide expression. Some of these changes appeared in the pre-symptomatic period and feeding behaviour was marked by increased food intake. Unfortunately, this study did not investigate the energy expenditure in ALS murine models. This could be the first proven link between modified food intake and hypermetabolism during ALS. In our study, the presence of hypermetabolism does not seem to modify the nutritional status of patients with ALS during follow-up. This result may be masked by our practice in referral ALS centres. Patients with ALS have a nutritional consultation every 3 months. Nutritionists are aware of the negative prognostic value of weight loss. As hypermetabolism can trigger weight loss, advice on diet is given and oral nutritional supplements are prescribed to prevent the deleterious effects of weight loss.

Conclusion

Hypermetabolism is present in more than half of this large cohort of patients with ALS. Patients with a $\Delta REE > 20\%$ tend to lose more weight on FM and have weaker respiratory muscles. A $\Delta REE > 20\%$ seems to influence the functional evolution of patients with ALS with a faster evolution of ALSFRS-R slope during follow-up. In addition, these patients tend to have a higher risk of death. The increase in REE:FM ratios is also positively associated with the risk of dying. All of this suggests that patients with hypermetabolism >20% of the theoretical value seem to be more at risk and should therefore receive more attention.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Correlations between ΔREE and quantitative baseline characteristics.
Table S2. Correlations between ΔREE and quantitative evolution during follow-up.

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