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1 **HYPERMETABOLISM IS A REALITY IN AMYOTROPHIC LATERAL**  
2 **SCLEROSIS COMPARED TO HEALTHY SUBJECTS**

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41 **Authors' contribution:**

42 PF, PJ, PC, JCD and BM designed research; PJ, PF, YB, SW, MC, PC and JCD conducted  
43 research; PJ, PF, YB, SW, MC and JCD provided essential materials (databases); AL, PJ and  
44 PF performed statistical analysis; PF, PJ, AL, PC, JCD wrote paper; PF and PJ had primary  
45 responsibility for final content. All authors read and approved the final manuscript.

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52 **Abbreviations**

53 ALS: amyotrophic lateral sclerosis

54 BMI: body mass index

55 CI: confidence interval

56 FM: fat mass

57 FFM: free fat mass

58 IC: indirect calorimetry

59 IQR: interquartile range

60 cREE: calculated resting energy expenditure

61 mREE: measured resting energy expenditure

62 REE: resting energy expenditure

63 RQ: respiratory quotient

64 TEE: total energy expenditure

65 **Abstract:**

66 Rationale: Hypermetabolism (HM) in Amyotrophic lateral sclerosis (ALS) is the reflection of  
67 a high energy metabolic level, but this alteration seems controversial. The main objective of  
68 the study was to confirm the existence of HM during ALS compared to healthy subjects.

69 Methods: A cohort of ALS patients was compared to a control group without metabolic  
70 disorder. The assessment included anthropometric criteria measurements, body composition  
71 by bioelectric impedance analysis and resting energy expenditure (REE) by indirect  
72 calorimetry. HM was defined as a variation  $> +10\%$  between measured and calculated REE.  
73 Statistical analysis used Mann-Whitney and Chi2 tests. Multivariate analysis included logistic  
74 regression.

75 Results: 287 patients and 75 controls were included. The metabolic level was higher in ALS  
76 patients (1500 kcal/24h [1290–1693] vs. 1230 kcal/24h [1000 –1455],  $p < 0.0001$ ) as well as  
77 the REE/fat free mass ratio (33.5 kcal/kg/24h [30.4 –37.8] vs. 28.3 kcal/kg/24h [26.1–33.6],  $p$   
78  $< 0.0001$ ). 55.0% of ALS patients had HM vs. 13.3% of controls ( $p < 0.0001$ ). HM was  
79 strongly and positively associated with ALS (OR= 9.50 [4.49 –20.10],  $p < 0.0001$ ).

80 Conclusions: HM in ALS is a reality, which affects more than half of the patients and is  
81 associated with ALS. This work confirms a very frequent metabolic deterioration during ALS.  
82 The identification of HM can allow a better adaptation of the patients' nutritional intake.

83 **Keywords:** Amyotrophic lateral sclerosis, hypermetabolism, resting energy expenditure

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## 89 **INTRODUCTION**

90 Amyotrophic lateral sclerosis (ALS) is a rare and severe neurodegenerative disease  
91 commonly diagnosed between the age of 65 to 70 years and whose incidence is 2 to 3 /  
92 100,000 person-years (1–5). Weight loss during ALS is associated with impaired functional  
93 status and quality of life (6,7). Undernutrition affects 9 to 55% of patients (7–10) and is an  
94 independent negative factor for survival (6). Undernutrition in ALS results from an  
95 imbalance between energy intake and total energy expenditure (TEE) (11,12). The resting  
96 energy expenditure (REE), component of the TEE, can be increased in ALS, and this increase  
97 corresponding if high, to hypermetabolism (HM) (7,13). HM is a persistent phenomenon  
98 during the course of the disease (14), and would concern 50 to 60% of patients (7,13). Only  
99 two studies, with a modest number of cases and a heterogeneous methodology, studied HM in  
100 ALS compared to a control group (13,15). Due to the disparate results of these works, the  
101 notion of HM in ALS is controversial.

102 In light of this controversy, the main objective of this study was to confirm the existence of  
103 HM during ALS compared to healthy subjects.

104

## 105 **METHODS**

### 106 **Inclusion criteria**

107 ALS patients included were followed up at the ALS Referral Centre and the Nutrition Unit of  
108 the University Hospital of Limoges (France), diagnosed between November 1996 and  
109 November 2014, according to Airlie House criteria (16). They were suffering from ALS alone

110 or associated with frontotemporal dementia and all were treated with riluzole. They could  
111 have a bulbar or limb onset form, a familial background (FALS) or sporadic form of ALS.  
112 Functional impairment was assessed by the ALS Functional Rating Scale (ALSFRS) or its  
113 revised form (ALSFRS-R) (17). REE was measured (mREE) by indirect calorimetry (IC),  
114 with a respiratory quotient (RQ) between 0.7 and 0.87 (7). Indeed, during an overnight fasting  
115 period from 7 to 14 hours, the RQ would be 0.68 to 0.90 (18). IC was performed less than 12  
116 months after diagnosis and less than 1.5 months after the nutritional assessment. The body  
117 composition was to be assessed by bioelectric impedance analysis (BIA), using the validated  
118 formula for ALS patients (19).

119 The control subjects, from the Human Nutrition Unit of the University of Clermont Auvergne  
120 (France), were healthy people without ALS and not suffering from a metabolic altering  
121 disease such as inflammatory bowel disease, cancer, dysthyroidism or infectious disease.  
122 Controls were assessed by IC and BIA, according to similar procedures to those used for  
123 patients, using Kyle et al. equation for the body composition determination (20,21).

#### 124 **Nutritional and metabolic assessment**

125 The nutritional and metabolic assessments, homogeneous and standardized in both centres,  
126 were performed according to standard procedures. Subjects were weighed in their underwear  
127 using a SECA<sup>TM</sup> electronic scale recording to 0.1 kg (Vogel & Halke, Hamburg, Germany) in  
128 an upright position or on a SECA<sup>TM</sup> weighing chair if they could not stand upright. Height  
129 was obtained using a SECA<sup>TM</sup> gauge recording to 0.2 cm (Vogel & Halke, Hamburg,  
130 Germany) in an upright position, or using the Chumlea formulas for people over 60 who  
131 could not be verticalized (22). Body mass index (BMI) was calculated as weight (kg) / height  
132 x height (m<sup>2</sup>). Fat free mass (FFM in kg) and fat mass (FM in kg) were obtained from  
133 bioelectric impedance analysis at 50 kHz after five minutes of rest in supine position. They



134 were calculated using validated formulas: Desport et al. equation for ALS patients (19) with  
135 an Analycor<sup>TM</sup> device (Eugédia, Chambly, France), and Kyle et al. equation (21) for controls  
136 with BIA 101<sup>TM</sup> (RJL System, Detroit, USA). The triceps skinfold (TSF), necessary for the  
137 FFM determination according to the Desport et al. formula (19), was obtained from the  
138 average of three measurements on each side with a Harpenden caliper (Baty International,  
139 Burgess Hill, UK) according to the usual modalities (23).

140 IC was performed in the morning after 12 hours overnight fasting in supine position and at  
141 rest, using the Quark RMR<sup>TM</sup> (Cosmed, Rome, Italy) and the Deltatrac II<sup>TM</sup> device  
142 (DatexEngström, Helsinki, Finland), after instruments calibration (24). The mean  
143 repeatability coefficient was 7,3 +/- 2%. Harris and Benedict 1919 (HB1919) formulas were  
144 used to calculate REE (cREE) (22). The percentage of REE variation ( $\Delta$ REE) was calculated  
145 using the formula:  $\Delta$ REE = (mREE [kcal / 24h] - cREE [kcal / 24h]) / cREE (kcal / 24h) \*  
146 100. HM was defined as  $\Delta$ REE > +10%.

#### 147 **Data collection and Statistical analysis**

148 All data were collected prospectively and extracted from the CleanWEB<sup>TM</sup> database of the  
149 Limoges ALS Referral centre and from the Human nutrition Unit Laboratory of Clermont-  
150 Ferrand databases, validated by the French Commission Nationale de l'Informatique et des  
151 Libertés. All subjects gave their informed consent for the data collection. The study was  
152 reported at ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT03382392).

153 Statistical analysis was performed using SAS<sup>TM</sup> 9.3 (SAS institute NC, Cary, USA).  
154 Comparative analyses were conducted on the ALS group versus the control group using the  
155 Mann-Whitney and the Chi2 tests. To investigate the factors associated with HM, a logistic  
156 regression model was conducted and results were expressed with odds ratio (OR) and 95%  
157 confidence interval (95%CI). Adjustment variables were sex, age, BMI, FFM and FM.

158 Covariates with a significance threshold  $p < 0.2$  in univariate analysis were included in  
159 multivariate analysis and a forward selection variable was used.

160

## 161 **RESULTS**

162 IC was performed on 405 ALS patients of which 118 were excluded: 35 for a RQ  $< 0.7$  or  $>$   
163  $0.87$ , 30 for a time lag between IC and nutritional assessment greater than 1.5 months, 25  
164 because the delay between diagnosis and IC was over 12 months and 28 because of a lack of  
165 BIA data (figure 1).

166 Seventy-five healthy controls were compared to 287 ALS patients. In ALS patients, 40.8 %  
167 had a bulbar form, and 9.4% a familial form. The median delay between diagnosis and  
168 nutritional assessment was 4.2 month [2.2–6.4]. The median ALSFRS-R score at inclusion  
169 was 39.6 points [35-43]. Characteristics and comparisons of ALS patients and controls are  
170 presented in table 1. The RQ was not significantly different between the two populations. The  
171 metabolic level was higher in ALS patients (1500 kcal/24h [1290–1693] vs. 1230 kcal/24h  
172 [1000 –1455],  $p < 0.0001$ ) as well as REE/FFM (33.5 kcal/kg/24h [30.4 –37.8] vs. 28.3 [26.1–  
173 33.6] kcal/kg/24h,  $p < 0.0001$ ). HM was significantly more frequent in ALS patients than in  
174 controls (55.0% vs. 13.3%,  $p < 0.0001$ ).

175 HM was not found in 129 patients (45,0%) and 65 controls (86,7%). In subjects not  
176 considered to be hypermetabolic, mREE was significantly higher in ALS patients compared  
177 to healthy controls (1331 kcal/24h [1153 –1543] vs. 1210 kcal/24h [981 –1450]),  $p = 0.0008$ )  
178 with a higher REE variation (1.8% [-3.5 –6.1] vs. -2.1% [-8.8 –1.4],  $p = 0.0001$ ). In the  
179 absence of HM, REE/ FFM ratio was higher in ALS patients (31.0 kcal/kg/24h [28.0 –35.0]  
180 vs. 28.1 kcal/kg/24h [25.8 –32.8],  $p = 0.0004$ ).

181 Factors associated with HM in univariate and multivariate analysis were presented in table 2.  
182 After adjustment, HM was positively associated with ALS ( $OR_{adjusted} = 9.50 [4.49 - 20.10]$ ,  $p$   
183  $< 0.0001$ ) and with being a male ( $OR_{adjusted} = 1.73 [1.10 - 2.72]$ ,  $p = 0.018$ ) (table 2).

184

## 185 **DISCUSSION**

186 This study highlights the existence of HM and the high level of metabolic alteration in a large  
187 cohort of ALS patients compared to healthy subjects. These metabolic alterations concern all  
188 patients, even in the absence of HM. It was essential for clinical practice to confirm the reality  
189 of HM during ALS. Indeed, these metabolic alterations can contribute to an increase in TEE  
190 (12). In the absence of adaptation of energy intake, an increase in TEE is a cause of weight  
191 loss and undernutrition, which are associated with impaired functional status, alteration of  
192 quality of life and decrease in survival (6,7,13). This reinforces the importance of metabolic  
193 assessment and nutritional care in ALS, as soon as the diagnosis is made, in order to adapt the  
194 level of dietary intake or enteral nutrition.

195 Our ALS patients sample is the largest in literature in this field. The original use of a logistic  
196 regression model clearly asserts a positive and strong association between ALS and HM,  
197 which has not been demonstrated previously. Indeed, Desport et al. described a higher mREE  
198 in 62 ALS patients versus 31 healthy volunteers, comparable on nutritional parameters, but  
199 the lack of multivariate analysis could not confirm the link between HM and ALS (13).  
200 Conversely, Vaisman et al. found a decrease in mREE in a modest population of 33 ALS  
201 patients compared to 33 controls: due to the disparity in weight, BMI and FFM between the  
202 two groups, and the lack of adjustment on these variables, the results were not interpretable  
203 (15).

204 Regardless of the relationship between HM and ALS, our study suggests a male influence on  
205 HM. Although FFM, which is proportionately higher in men (20) and the main determinant of  
206 REE (15,26), this relationship is not explained in this study by a difference in body  
207 composition by gender. Indeed, body composition parameters were not associated with HM in  
208 this work.

209 The causes of the HM remain unknown. Several hypotheses are mentioned: increased glucose  
210 and lipids consumption, mitochondrial alterations, hypothalamic dysfunction (6,27). Due to  
211 the high frequency of metabolic changes in ALS, HM can certainly be considered a marker of  
212 the disease. The identification of metabolic pathways and the search for biomarkers of HM  
213 would likely improve the understanding of physiopathological mechanisms and propose new  
214 therapeutic pathways targeted at metabolic phenotype in ALS.

215 Our study presents limitations. Despite the large number of patients followed by the ALS  
216 Referral center (88.2% of patients from our region) (7), the data were not extracted from a  
217 register and were therefore not totally exhaustive. It would have been preferable to have a  
218 larger control population from the same center and matched on the patients. We did not have  
219 such a control cohort in our center, and we used the control population which seemed to us  
220 the most suitable. So, even if patients and controls were assessed in two different centers and  
221 regions, these bordering regions (Limousin and Auvergne) had a comparable gender and age  
222 distribution ratio according to the French National Institute of Statistics (28). Moreover,  
223 nutritional and metabolic assessments were performed under standardized conditions in both  
224 center, and body composition was obtained from crude impedancemetric data (impedance and  
225 reactance), using validated formulas for each group: Desport et al. formula for ALS patients,  
226 validated versus the reference method (Dual x-ray absorptiometry) (19) and Kyle et al.  
227 formula for controls, suitable for body composition assessment in elderly subjects (21). Due  
228 to the unavailability of the same device in each center, two different devices were used for IC.

229 However, the mREE values of its two devices were recognized as very similar in a previous  
230 work (29). Even if age and BMI were different between patients and controls, we have taken  
231 into account these variances, which have been minimized by adjustment in multivariate  
232 analysis. We chose not to consider the subtype of ALS (clinical phenotype; familial versus  
233 sporadic form), the fasciculations and the tobacco consumption for adjustment, since previous  
234 works found no influence for these criteria on the metabolic changes (6,7,13). Finally, even if  
235 autonomic nervous abnormalities with a potential influence on the metabolic level were  
236 described in ALS, manifested for example by an increase in blood pressure or resting heart  
237 rate (30,31), we did not have such data to make an adjustment.

238 The use of HB1919 formulas, established for healthy subjects, can be another bias. Indeed, it  
239 is possible that the  $\Delta$ REE demonstrated was related to an inappropriate use of these equations  
240 in ALS patients. Nevertheless, in a recent work, Jesus et al. compared the mREE and cREE  
241 by 12 predictive formulas, including HB1919 equations (32): This work highlighted that ALS  
242 patients had a mREE higher than cREE whatever the formula used, and therefore that the  
243 increase in REE was not related to the inappropriate use of HB1919 equations. Thus, these  
244 formulas seem to be relevant as a reference value to search for an  $\Delta$ REE. Furthermore, other  
245 authors have validated, for ALS patients, the use of equations comprising sex and age, such as  
246 HB1919 or Mifflin-St Jeor formulas, both for the REE measurement (33), but also in models  
247 allowing to estimate the TEE (12).

248 Our study focused specifically on the REE assessment, which is not sufficient on its own to  
249 define the energy requirements of patients. We didn't studied the TEE, which is a basis for  
250 estimating energy requirements. Thus, in a previous work, Kasarskis et al. proposed models  
251 for estimating the TEE, which can be used in current practice, taking into account body  
252 composition and physical function, making it possible to adapt food or enteral intakes (12).

253 At last, this study cannot specify when the metabolic changes appear. It could be of interest to  
254 measure REE in the presymptomatic stage in descendants of ALS familial form patients, in  
255 order to detect a possible HM before onset of the first symptoms and to set up early  
256 nutritional care.

257

## 258 **CONCLUSION**

259 The concept of HM during ALS is a reality and could not be controversial: HM affects more  
260 than half of the patients and is positively and strongly associated with ALS. This work  
261 confirms a very frequent metabolic alteration during ALS, contributing to the deterioration of  
262 nutritional status, a factor of poor prognosis. This reinforces the importance of HM screening,  
263 which should be systematic, to provide early and appropriate nutritional care: diet advice, oral  
264 supplementation or enteral nutrition. The causes of HM are still unknown. The identification  
265 of the mechanisms involved could improve patient management.

266

## 267 **Conflicts of interest**

268 The authors have no conflict of interest to disclose

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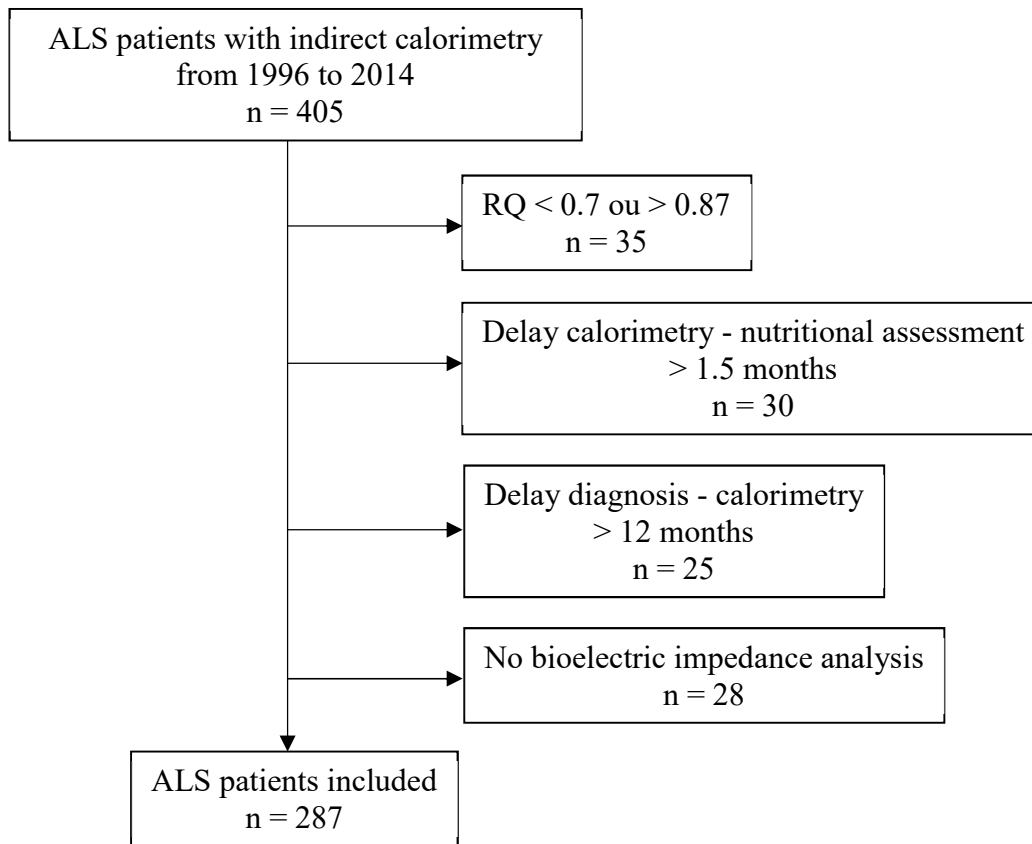
377 **Figure legend**

378 Figure 1: Flowchart of ALS patients included in the study.

379 ALS: amyotrophic lateral sclerosis; RQ: respiratory quotient

380

**Figure 1:**



**Table 1:** Comparison of demographic, nutritional characteristics and resting energy expenditure (REE) between ALS patients and healthy controls

| Variables                | ALS Patients                       | Healthy controls                  | p                 |
|--------------------------|------------------------------------|-----------------------------------|-------------------|
|                          | Median [IQR] or n (%)<br>(n = 287) | Median [IQR] or n (%)<br>(n = 75) |                   |
| Male                     | 145 (50.5)                         | 40 (53.3)                         | 0.66              |
| Age at IC (years)        | 66.4 [56.7–73.1]                   | 75.0 [68.5–86.0]                  | <b>&lt;0.0001</b> |
| Weight (kg)              | 64.9 [57.9 –74.2]                  | 66.0 [54.5 –75.0]                 | 0.25              |
| BMI (kg/m <sup>2</sup> ) | 24.3 [22.0 –27.5]                  | 26.2 [23.2 –28.4]                 | <b>0.026</b>      |
| FFM (kg)                 | 44.4 [36.9 –51.8]                  | 40.7 [30.9 –54.8]                 | 0.15              |
| FM (kg)                  | 20.7 [15.2 –25.4]                  | 20.5 [16.8 –26.9]                 | 0.56              |
| mREE (kcal/24h)          | 1500 [1290 –1693]                  | 1230 [1000 –1455]                 | <b>&lt;0.0001</b> |
| cREE (kcal/24h)          | 1327 [1195 –1496]                  | 1262 [1023 –1460]                 | <b>0.0015</b>     |
| $\Delta$ REE (%)         | 11.5 [3.6 –19.3]                   | -1.2 [-7.5 –5.3]                  | <b>&lt;0.0001</b> |
| Hypermetabolism          | 158 (55.0)                         | 10 (13.3)                         | <b>&lt;0.0001</b> |
| REE/weight (kcal/kg/24h) | 22.9 [20.9 –25.0]                  | 19.2 [17.4 –20.9]                 | <b>&lt;0.0001</b> |
| REE/FFM (kcal/kg/24h)    | 33.5 [30.4 –37.8]                  | 28.3 [26.1–33.6]                  | <b>&lt;0.0001</b> |

*ALS: amyotrophic lateral sclerosis; BMI: body mass index; FFM: free fat mass; cREE: calculated resting energy expenditure;  $\Delta$ REE: percentage of REE variation; FM: fat mass; IC: indirect calorimetry; IQR: interquartile range; mREE: measured resting energy expenditure; n: number*

**Table 2:** Factors associated with hypermetabolism

| Variables                 | Univariate analysis         |                   | Multivariate analysis          |                   |
|---------------------------|-----------------------------|-------------------|--------------------------------|-------------------|
|                           | OR <sub>crude</sub> [95%CI] | p                 | OR <sub>adjusted</sub> [95%CI] | p                 |
| ALS patients vs. controls | 7.96 [3.93 – 16.12]         | <b>&lt;0.0001</b> | 9.50 [4.49 – 20.10]            | <b>&lt;0.0001</b> |
| Male vs. female           | 1.50 [0.99 – 2.28]          | 0.054             | 1.73 [1.10 – 2.72]             | <b>0.018</b>      |
| Age (+ 1 year increment)  | 0.98 [0.97 – 1.00]          | 0.061             | 1.01 [0.99 ; 1.03]             | 0.250             |
| BMI (+ 1 point increment) | 0.96 [0.92 – 1.00]          | 0.070             |                                |                   |
| FFM (+ 1 kg increment)    | 1.02 [1.00 – 1.04]          | 0.064             |                                |                   |
| FM (+ 1 kg increment)     | 0.97 [0.95 – 1.00]          | <b>0.023</b>      |                                |                   |

OR: odds ratio; CI: confidence interval; ALS: amyotrophic lateral sclerosis; BMI: body mass index;

FFM: free fat mass; FM: fat mass