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Dyslipidemia is a protective factor in amyotrophic lateral sclerosis



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ABSTRACT

Background: Amyotrophic lateral sclerosis (ALS) is the most serious form of degenerative motor neuron disease in adults, characterized by upper and lower motor neuron degeneration, skeletal muscle atrophy, paralysis, and death. High prevalence of malnutrition and weight loss adversely affect quality of life. Moreover, two thirds of patients develop a hypermetabolism of unknown cause, leading to increased resting energy expenditure. Inasmuch as lipids are the major source of energy for muscles, we determined the status of lipids in a population of patients with ALS and investigated whether lipid contents may have an impact on disease progression and survival.

Methods: Blood concentrations of triglycerides, cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were measured in a cohort of 369 patients with ALS and compared to a control group of 286 healthy subjects. Postmortem histologic examination was performed on liver specimens from 59 other patients with ALS and 16 patients with Parkinson disease (PD).

Results: The frequency of hyperlipidemia, as revealed by increased plasma levels of total cholesterol or LDL, was twofold higher in patients with ALS than in control subjects. As a result, steatosis of the liver was more pronounced in patients with ALS than in patients with PD. Correlation studies demonstrated that bearing an abnormally elevated LDL/HDL ratio significantly increased survival by more than 12 months.

Conclusions: Hyperlipidemia is a significant prognostic factor for survival of patients with amyotrophic lateral sclerosis. This finding highlights the importance of nutritional intervention strategies on disease progression and claims our attention when treating these patients with lipid-lowering drugs. **Neurology® 2008;70:1004-1009**

GLOSSARY

AD = Alzheimer disease; **ALS** = amyotrophic lateral sclerosis; **ALS-FRS** = ALS functional rating scale; **BMI** = body mass index; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **PD** = Parkinson disease.

Amyotrophic lateral sclerosis (ALS) is a chronic, adult-onset neurodegenerative disorder affecting both the lower motor neurons in the spinal cord and brainstem and the upper motor neurons in the motor areas of the cerebral cortex and leading to death within 2 to 5 years of onset through failure of the respiratory muscles.¹

Despite the traditional view of ALS as a pure motor neuron disorder, growing evidence suggests that the disease is, in fact, a multisystem disorder with additional extramotor neurologic manifestations. Beyond the nervous system, intriguing metabolic alterations have also been observed in association with the course of the disease.² In particular, recent studies revealed that two thirds of patients with ALS present with a stable hyper-

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metabolism that correlates with survival.³⁻⁵ Consistently, ALS animal models present with reduced adiposity and increased rates of energy expenditure⁶ and increasing the lipid content of the diet offers neuroprotection and extends survival in these models,^{6,7} whereas restricting calorie intake exacerbates the motor symptoms.⁸

Whether any kind of perturbation of lipid metabolism does exist in patients with ALS that could have an impact on disease progression and survival has never been investigated. Here, we determined the status of lipids in a large cohort of patients with ALS at both the biochemical and histologic level, and correlated different lipid values with the patients' survival times.

METHODS Patients. Two independent cohorts of patients were included in this study. Serum lipid concentrations were determined in 369 patients who met the El Escorial World Federation of Neurology criteria for the diagnosis of definite or probable ALS⁹ at the time of blood sampling. Signed consent was not requested for the lipid dosages because in France studies implying "one more blood sample" added to a systematic blood sampling do not require Institutional Review Board approval. The control group was composed of 286 age- and sex-matched patients who attended the hospital for routine lipoprotein profile analysis. Those subjects hospitalized in the Lipid and Metabolism Unit were not accepted. Patients with diabetes or hepatic disease were excluded from both groups, and patients with ALS treated with lipid-lowering drugs were assayed only after 2 months of washing out. Blood samples were taken as a part of the initial clinical evaluation routinely performed for both patients with ALS and control subjects. After sampling, patients were followed up during a mean period of 23.9 months (median = 15 months). Death was confirmed by death certificate or written letter from relatives or physicians. Information was obtained for all patients. At the end of the study (June 30, 2004), 318 patients with ALS (86.2%) were dead, and 51 (13.8%), still alive, were censored. Survival times were calculated as the duration between the onset of the first symptoms and death or censoring.

A second cohort of patients was constituted for a retrospective study on the histopathologic records of 59 autopsy-confirmed patients with ALS and 16 autopsy-confirmed patients with Parkinson disease (PD), the latter considered as a control group. All patients died at the Hôpital de la Pitié-Salpêtrière (Paris, France) between 1983 and 2005 and gave signed informed consent for autopsy.

Biochemical¹⁰ and histologic procedures. Detailed methods are available on the *Neurology*[®] Web site at www.neurology.org.

Statistical analysis. Measures of association between pairs of nominal categorical variables were analyzed by the contingency coefficient (cc) with exact *p* value using the

Table 1 Lipidemia in the cohort 1 patients with amyotrophic lateral sclerosis (ALS) and control subjects

Item	Control (n = 286)	ALS (n = 369)
Total cholesterol (g/L)	2.1 ± 0.5	2.5 ± 0.5*
Triglycerides (g/L)	1.3 ± 0.8	1.3 ± 0.9
HDL (g/L)	0.6 ± 0.2	0.6 ± 0.15
LDL (g/L)	1.2 ± 0.4	1.6 ± 0.4*
LDL/HDL ratio	2.1 ± 0.9	2.9 ± 1.2*
% of individuals with increased total cholesterol	11.2	23.8*
% of individuals with increased triglycerides	25.9	21.4
% of individuals with increased HDL	19.6	11.7*
% of individuals with increased LDL	20.3	48.9*

Data are expressed in g/L or in percentages of the total number of patients in each group.

**p* < 0.0001 vs control.

†*p* < 0.006 vs control.

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

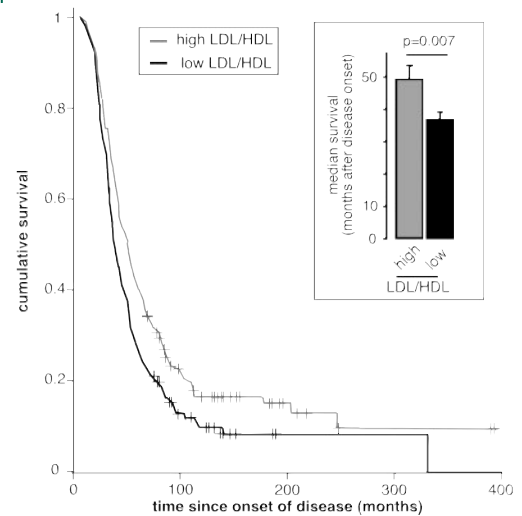
Statexact version 4.01 software. Comparisons of means between continuous demographic data were performed by one-way analysis of variance. The degree of correlation (*r*) between continuous variables was also calculated. For survival analysis, patients were dichotomized into two groups: low low-density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio (equal or below the cutoff defined as the LDL/HDL ratio mean value in the ALS group) and high LDL/HDL ratio (above the cutoff). Survival curves for the dichotomized prognostic variable were compared by the Mantel Cox (log rank) statistic, without stratification. The prognostic value of this parameter was determined by univariate Cox proportional hazard analysis. Mean occupancy of fatty lesions was compared using Student *t* test. Differences were considered significant at *p* < 0.05 (two-sided). Data are expressed as mean ± SD. Analyses were performed with SPSS version 11.0 software.

RESULTS Blood lipid levels in patients with ALS (cohort 1). Male-to-female sex distribution was 1.3:1 and limb onset vs bulbar onset was 3:1. At the time of blood sampling, mean age was 57.5 ± 13.0 years and body mass index (BMI) was 24.6 ± 3.4 kg/m². The data are in close accordance with previous reports,^{1,11} thus showing that the patients included in the present study are representative of the ALS population. The mean values of the measured blood lipids values are provided in table 1. Levels of total cholesterol were significantly higher in patients with ALS than in control subjects of 19%, while those of LDL were increased of 33% and the mean LDL/HDL ratio of 38%. Triglyceride and HDL levels remained un-

changed. We then classified patients in the two groups as being normolipidemic or hyperlipidemic in agreement with age- and sex-matched standards typically used in clinical practice (table e-1). The percentages of individuals falling into the hyperlipidemic category for each measured variable are provided in table 1. The proportions of patients with increased total cholesterol or LDL levels were significantly more important in the ALS population than in the control group. In contrast, the proportion of increased HDL levels was significantly lower in ALS than in control patients. Accordingly, when we classified patients in the two groups as having low LDL/HDL ratio (equal or below the cutoff defined as the LDL/HDL ratio mean value in the ALS group, that is 2.99) or high LDL/HDL ratio (above the cutoff), we found that 45.4% of patients with ALS, but only 16.1% of control subjects, presented with a high LDL/HDL ratio ($p < 0.0001$).

LDL/HDL ratio and survival of patients with ALS. Patients with ALS with high LDL/HDL ratio (as defined above) lived longer than those having low LDL/HDL ratio. After adjustment with the Cox proportional hazard model, the p value was equal to 0.007 with a relative risk of 1.35 (95% CI: 1.08 to 1.69), which means that low LDL/HDL ratio patients with ALS exhibit 35% increased risk of death (figure 1). Median survival was significantly higher in high LDL/HDL ratio patients with ALS (49.2 ± 4.2 months) than in low LDL/HDL ratio patients with ALS (36.7 ± 2.7 months, figure 1, inset). To check whether initial differences between the two subgroups of patients with ALS could have accounted for the increase in survival, we compared them at the time of blood sampling. The monitoring of disease severity, based on the ALS functional rating scale (ALS-FRS), revealed no differences in the degree of motor disability. On the other hand, body mass, BMI, and lipid profile, already augmented in the high LDL/HDL ratio subgroup, appeared, in fact, not reduced in low LDL/HDL ratio patients with ALS, as compared to the control population, clearly indicating that none of the ALS subgroups showed signs of malnutrition at inclusion (table 2). To assess a dose response effect of the LDL/HDL ratio on survival, we tested a series of cut points for LDL/HDL ratio and calculated the values of exponential beta, 95% interval for exponential beta, and p value for these different cut points. As shown in table e-2, there was a clear dose response effect of the LDL/HDL ratio on survival in our study.

Figure 1 Correlation between low-density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio and survival in patients with amyotrophic lateral sclerosis (ALS)



Kaplan-Meier survival curves of patients with ALS stratified according to their LDL/HDL ratio. The black line represents patients with ALS having low LDL/HDL ratio (equal or below the cutoff defined as the LDL/HDL ratio mean value in the ALS group, that is 2.99). The light gray line represents patients with ALS having high LDL/HDL ratio (above the cutoff). Censored patients are indicated by (+) symbols on the corresponding survival curve. Inset: median survival times of low and high LDL/HDL ratio patients with ALS.

Hepatic steatosis in patients with ALS (cohort 2). Hyperlipidemia is thought to be a major cause of hepatic steatosis. We therefore asked whether the hyperlipidemia of patients with ALS might trigger hepatic steatosis, by comparing semiquantitatively the incidence and extent of fatty accumulations in autopsic liver specimens from 59 patients with ALS and 16 patients with PD. In this second ALS cohort, male-to-female sex distribution was 1.8:1, and limb onset vs bulbar onset was 2.6:1. Mean age at the time of death was 65.2 ± 1.8 years. The detailed histologic examination of the liver specimens is reported in table e-3. The weight of the liver did not differ between the two groups ($t = 1.34$; $p = 0.183$), although one of the patients with ALS had enlarged fatty liver (4,000 g). The frequency of hepatic steatosis was similar between both groups (46 out of 59 cases for patients with ALS, and 12 out of 16 cases for patients with PD, that is about 77% of cases). On the contrary, the extent of the lesions was much more pronounced in patients with ALS than in patients with PD (figure 2A). Two representative ALS cases are shown in figure 2: one case of severe steatosis ($>80\%$; figure 2B), and another one of moderate steatosis ($<20\%$; figure 2, C and D).

Table 2 Metabolic and clinical features in low and high low-density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio patients with amyotrophic lateral sclerosis (ALS) and in control subjects

Item	Control (n = 286)	ALS	
		Low LDL/HDL (n = 201)	High LDL/HDL (n = 167)
Body mass (kg)	ND	67.1 ± 12.0	71.7 ± 11.9*
BMI (kg/m ²)	ND	24.1 ± 3.3	25.3 ± 3.3*
ALS-FRS	ND	30.4 ± 8.1	30.3 ± 7.5
Total cholesterol (g/L)	2.10 ± 0.47	2.34 ± 0.46*	2.67 ± 0.42**
LDL (g/L)	1.21 ± 0.39	1.44 ± 0.34*	1.87 ± 0.35**
HDL (g/L)	0.63 ± 0.22	0.81 ± 2.10	0.48 ± 0.10**
Triglycerides (g/L)	1.30 ± 0.76	1.16 ± 1.09	1.55 ± 0.59**

* $p < 0.0001$ vs low LDL/HDL.

** $p < 0.05$ vs control.

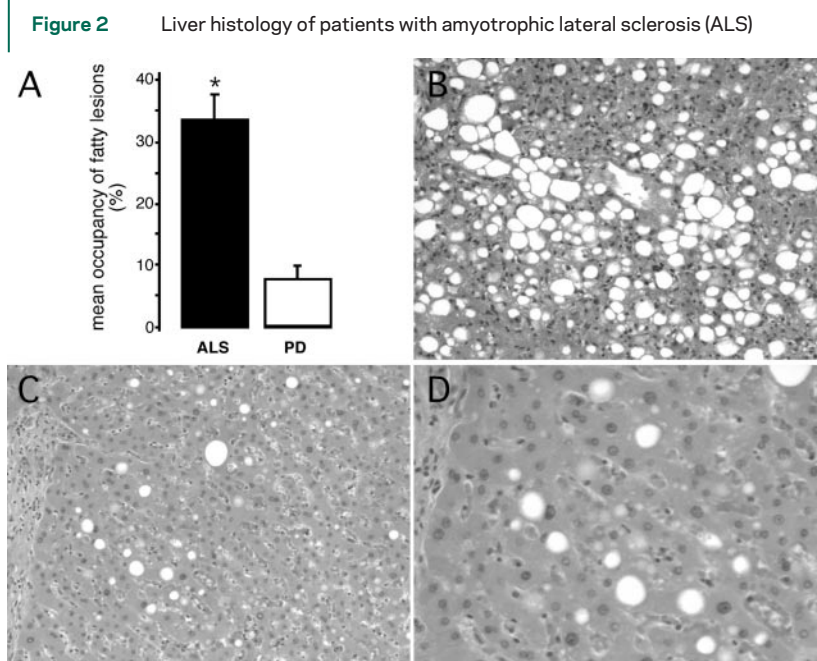
ND = not determined; BMI = body mass index; ALS-FRS = ALS functional rating scale.

DISCUSSION The present study demonstrates that hyperlipidemia is a typical feature of ALS. As a consequence, the extent of fatty accumulations in the liver is particularly more elevated in this disease than in other neurologic disorders such as PD. Most importantly, we also show that the observed hyperlipidemia is a prognostic factor for the survival of patients with ALS.

Several early studies have already reported the presence of hypertriglyceridemia and insulin resistance in a few cases of motor neuron disease.¹²⁻¹⁴ Our present findings provide further

evidence of the influence of peripheral lipidic abnormalities on the course of ALS. Of importance, such metabolic perturbations have been traditionally considered as being detrimental to neurodegeneration.¹⁵ For instance, the hyperinsulinemia observed in patients with Alzheimer disease (AD) increases the plasma levels of toxic A β , and is likely to worsen their cognitive performance.¹⁶⁻¹⁸ Studies on genetic animal models of AD have also shown the harmful effects of a high fat regimen,^{19,20} whereas restricting calorie intake alleviates neurodegeneration in several experimental models.^{21,22} As far as ALS is concerned, increasing the lipid content of the diet offers neuroprotection and extends survival in animal models of the disease^{6,7} but, on the contrary, calorie restriction exacerbates the motor symptoms.⁸ Although taking into account obvious interspecies differences, there are still several correlates between the ALS-like pathology in mutant SOD1 mice and the human disease. First, in both conditions, increased resting energy expenditure is a typical feature of the pathologic process.³⁻⁶ Second, this hypermetabolic trait is accompanied in mice by an augmented peripheral (muscular) clearance of lipids.²³ In man, an increased uptake of glucose and long chain fatty acids from arterial blood was shown to occur in denervated muscles of a few cases of ALS.²⁴ Finally, we show now that hyperlipidemic patients live longer, as do mutant SOD1 mice when fed with a high fat regimen.^{6,7}

What triggers hyperlipidemia in ALS is currently unknown and puzzling, especially because these patients are rather lean than obese, which could have simply explained the occurrence of hyperlipidemia or insulin resistance. One could envisage that it is the regenerative effort of denervating muscles that promotes an increasing



(A) Quantification of the extent of hepatic steatosis in autopsic liver specimens from patients with ALS and patients with Parkinson disease. * $p < 0.001$. (B) Severe macrovacuolar steatosis (>80% of total surface) in the liver of a patient with ALS ($\times 100$). (C) Moderate microvacuolar and macrovacuolar steatosis (<20% of total surface) in the liver of a patient with ALS ($\times 100$). (D) Higher magnification of panel C showing microvacuolar and macrovascular fatty accumulations ($\times 200$).

energetic demand, most likely in the form of lipids. Indeed, the lipid profile of patients with spinal cord injury is quite similar to that observed in the present study. After spinal cord immobilization, muscle disuse can reduce energy needs, and hence trigger hyperlipidemia and insulin resistance.^{25,26} Nevertheless, these patients present with decreased energy expenditure as a result of the reduced locomotor activity,²⁷ which clearly contrasts with that observed in patients with ALS.³⁻⁵ In addition, if hyperlipidemia in ALS was the consequence of decreased muscle usage, one could expect that blood lipids negatively correlate with the functional status of patients. Our own data (table 2) however showed no differences when comparing the degree of motor disability between low and high LDL/HDL ratio patients with ALS. Thus, progressive muscle atrophy and the subsequent decrease in energy demand cannot simply account for the hyperlipidemia associated with ALS. Certainly, further research at the molecular level is needed to gain insight into the relationships between ALS and metabolism.

The current study provides evidence that specific systemic metabolic alterations may impact the neurodegenerative process of ALS. The beneficial effect of hyperlipidemia on survival of more than 12 months is, to our knowledge, one of the most important documented. It has to be compared to the effect of riluzole, the only drug known to delay disease progression by several months. Our findings also warn against the use of lowering-lipid drugs in this vulnerable population of patients. Medications for the treatment of diseases such as diabetes and hypercholesterolemia, by acting on the energy balance, could interfere with the progression of ALS. It is therefore necessary to determine whether these very commonly prescribed drugs have an effect, either positive or negative, on the course of the disease. Finally, we strongly recommend surveillance of nutritional status as a priority task in the multidisciplinary management of patients with ALS.

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