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Hypolipidemia in Patients with Amyotrophic Lateral Sclerosis: A Possible Gender Difference?

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Background and Purpose We compared the levels of serum lipid, protein, and glucose between patients with amyotrophic lateral sclerosis (ALS) and healthy controls.

Methods The serum levels of lipids [including triglycerides, cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL)], protein, and glucose of 95 patients with ALS (60 men) were compared with those of 99 age- and sex-matched healthy controls (64 men). Both groups had normal dietary intakes.

Results Total cholesterol (p=0.004), LDL (p=0.040), triglyceride (p=0.025), and protein (p=0.010) levels, and LDL/HDL ratios (p<0.001) in men with ALS were significantly lower than those in their control counterparts. There were no such significant differences in these parameters between female patients with ALS and female controls.

Conclusions The serum levels of lipid and protein were significantly lower in male patients with ALS than in the male controls. Since we controlled for the confounding effects of dietary intake, hypolipidemia in ALS might be associated with the pathophysiology of the disease rather than being the result of the decreased dietary intake in ALS patients. Metabolic demand might increase in ALS, and it may be affected by gender. **J Clin Neurol 2013;9:125-129**

Key Words amyotrophic lateral sclerosis, dyslipidemia, gender differences.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that involves mainly the motor neurons in the cerebral cortex, brainstem, and spinal cord. Patients with ALS present with muscle paralysis, dysarthria, dysphagia, and respiratory dysfunction, which eventually lead to a bed-ridden state and the need for mechanical ventilation. Until recently, ALS was recognized as a disease that exclusively involves motor neurons;[1,2] however, many recent studies have revealed that the extramotor system[3] and extraneuronal systemic factors such as serum levels of lipids, apolipoprotein, and homocysteine might play an important role in the pathogenesis of ALS.[4-6] Among these extraneuronal systemic factors, serum lipid levels may be of particular importance because recent studies have demonstrated that dyslipidemia is a significant prognostic factor for ALS.[4] Despite the importance of serum lipid levels in ALS, conflicting results have been reported on the basal serum lipid levels in humans[4,7-9] and in an experimental model,[10,11] and between studies on ALS patients with diverse inclusion criteria.[4,7-9]

The primary aim of the present study was to address these discrepancies by evaluating the basal serum lipid levels of ALS patients in a well-controlled population without dysphagia, dementia, or the presence of a Levin or percutaneous endoscopic gastrostomy (PEG) tube, all of which can affect serum lipid

levels. The impact of gender differences on basal serum lipid levels in patients was also investigated.

Methods

Patients

This was a retrospective study that examined the medical information of 551 patients suspected of having motor neuron disease (MND) at their first visit to the ALS Clinic at the Seoul National University Hospital between January 2001 and July 2007. Among these patients, 456 were excluded because they did not meet the El Escorial criteria[12] for definite or probable ALS, or else a detailed record of their serum lipid concentrations was not available. Other exclusion criteria were as follows: ALS for more than 3 years; significant dysphagia; presence of a Levin or PEG tube; age <30 years or >70 years at disease onset; comorbidity with depression, diabetes, hepatic disease, dementia, malignancy, thyroid disease, or other evidence of recent systemic illness (e.g., pneumonia) that could potentially affect systemic metabolism; a family history of MND; any hereditary disease with probable association with MND (e.g., Sandhoff disease) or hereditary spastic paraplegia; and medication history of lipid-lowering drugs (Fig. 1). Serum levels of cholesterol, triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), LDL/HDL ratio, glucose, and protein were evaluated. The final data set comprised 95 ALS patients and 99 randomly selected healthy age- and sex-matched controls who had visited the hospital for routine health-care screening. Blood samples were taken as part of the initial routine clinical evaluation for both patients with ALS and the control subjects, and sampling was performed in the morning after a midnight "nil per os" instruction.

Statistical analysis

The mean serum levels of cholesterol, TG, lipoproteins, glucose, and proteins were compared between all ALS patients and the controls. Furthermore, the serum metabolites were compared between male and female ALS patients and the corresponding controls. The statistical analyses were performed using Student's *t*-test (Statistical Package for the Social Sciences version 17.0, IBM Corporation, New York, NY, USA), and the level of statistical significance was set at $p<0.05$.

Results

Basal levels of serum metabolites in ALS patients and controls

The basal levels of serum metabolites in ALS patients and con-

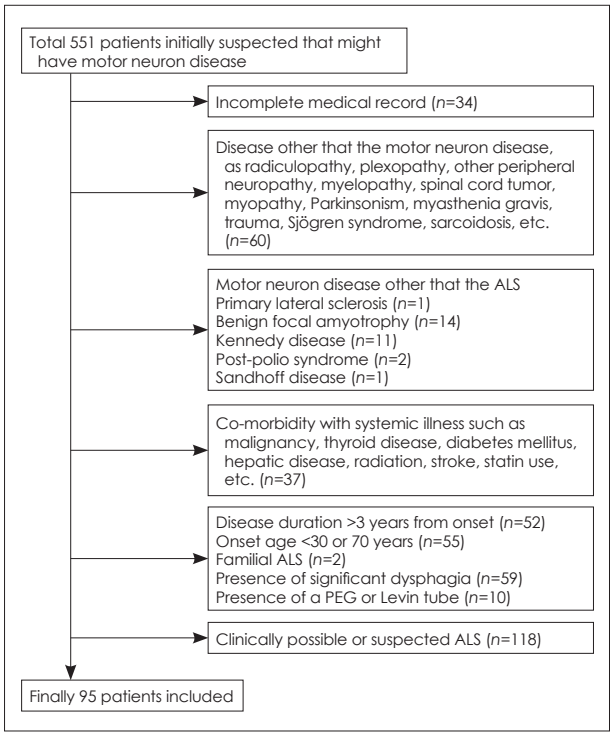

Fig. 1. ALS: amyotrophic lateral sclerosis, PEG: percutaneous endoscopic gastrostomy.

Table 1. Basal serum levels of lipids, proteins, and glucose in amyotrophic lateral sclerosis patients and age- and sex-matched controls

	Patients	Controls	*p*
n	95	99	
Age (years)	54.14±9.88	52.52±9.02	0.230
Males : females	60 : 35	64 : 35	0.830
Cholesterol (mg/dL)	188.17±33.93	197.76±30.08	0.038*
LDL (mg/dL)	115.56±28.72	120.24±26.49	0.239
HDL (mg/dL)	47.28±12.14	46.21±13.37	0.560
Triglycerides (mg/dL)	126.73±73.86	156.08±135.08	0.064
LDL/HDL ratio	2.58±0.88	2.87±1.02	0.035*
Protein (g/dL)	7.11±0.48	7.29±0.37	0.006*
Glucose (mg/dL)	98.49±24.21	98.86±21.49	0.907

*Statistically significant difference ($p<0.05$). Data presented as mean±standard deviation.
HDL: high-density lipoprotein, LDL: low-density lipoprotein, *n*: number.

trols are listed in Table 1. The serum levels of cholesterol and protein, and the LDL/HDL ratio were significantly lower in ALS patients than in control subjects. Serum TG levels also tended to be lower in the ALS group than in the control group, but the difference did not reach statistical significance (p<0.10).

Basal levels of serum metabolites in men with ALS and their control counterparts

The basal serum metabolite levels of 60 men with ALS and 64 age-matched male controls were compared (Table 2). The serum levels of cholesterol, LDL, TG, and protein, and the LDL/HDL ratio were all significantly lower in men with ALS than in healthy men.

Basal levels of serum metabolites in women with ALS and their control counterparts

There were 35 women with ALS and 35 healthy control women. In contrast to the results for men, the basal levels of serum metabolites in women with ALS did not differ significantly from those of age-matched female controls (Supplementary Table 1).

Discussion

In this study it was found that male ALS patients had hypolipidemia even when their dietary intake was intact. We controlled for the confounding effects of dietary intake on serum metabolites by excluding patients with significant dysphagia, depression, and dementia, and those who were fed via a Levin or PEG tube.[4] In addition, all included subjects fasted between midnight and the blood test to prevent the known effect of food ingestion on serum lipid levels. Under this restricted condition, the observation of hypolipidemia in ALS patients, together with the previous finding of increased peripheral lipid clearance in a mouse model of ALS,[13] indicate that the higher metabolic demand could be associated with the pathophysiology of ALS. In addition, the present finding that ALS is associated with hypolipidemia is consistent with previous results found in studies on ALS in mice, and concurs with the finding of another study showing that this vascular risk factor can be beneficial in patients with ALS.[9]

Metabolic deterioration in ALS has been reported previously.[10,14,15] However, only Dupuis et al.[4] and Chiò et al.[7] have assessed the levels of systemic metabolites in a sufficient number of patients. In contrast to our results, those obtained by Dupuis et al. and Chiò et al. showed that ALS patients had hyperlipidemia[4] and normolipidemia,[7] respectively. We believe that this difference could be attributable to these previous studies not controlling for the confounding variables that can affect the level of serum lipids, as mentioned in the Methods section of this study. In addition, the following findings of several previous studies support our finding that hypolipidemia might be a typical characteristic of ALS. First, ALS is associated with increased energy expenditure, which might lead to a depletion of serum lipid in these patients.[9,14,16-18] Second, studies using a mouse model of ALS have demonstrated increased peripheral lipid clearance and/or hypolipidemia in these animals.[10,11,13] Third, hyperlipidemia was positively correlated with survival and a slower rate of disease progression; the authors of these studies recommend a high fat-containing diet for patients with ALS.[4,10,14,19]

Another finding of our study was a difference in the observation of hypolipidemia in male and female ALS patients. Severe decreases in serum lipid and protein levels were observed in men with ALS; in contrast, women with ALS did not significantly differ from their age-matched controls in this regard. This result was consistent with those of a previous study on ALS mice.[11] The exact cause of this phenomenon is unclear. However, this gender difference might be associated with previous studies finding that knockout of the male liver X receptor beta gene, which is associated with cholesterol metabolism in the central nervous system, produces symptoms similar to MND only in male mice,[20] and that estrogen delays disease progression in ALS mice.[20,21] In addition, the association be-

Table 2. Basal serum levels of lipids, proteins, and glucose in men with amyotrophic lateral sclerosis, and sex-matched controls

	ALS (males)	Controls (males)	p
n	60	64	
Age (years)	54.45±10.53	52.54±9.37	0.289
Cholesterol (mg/dL)	179.90±29.39	196.03±31.69	0.004*
LDL (mg/dL)	109.85±25.61	120.09±28.96	0.040*
HDL (mg/dL)	45.30±12.69	44.00±13.87	0.588
Triglycerides (mg/dL)	124.05±55.87	169.86±146.30	0.025*
LDL/HDL ratio	2.59±0.93	3.22±0.87	<0.001*
Protein (g/dL)	7.07±0.51	7.29±0.42	0.010*
Glucose (mg/dL)	100.80±26.19	102.79±25.23	0.666

*Statistically significant difference (p<0.05). Data presented as mean±standard deviation.
HDL: high-density lipoprotein, LDL: low-density lipoprotein, *n*: number.

tween gender and serum lipid levels might be due to the predilection toward a greater prevalence of ALS among men[22] and the earlier onset and shorter survival time seen in transgenic male ALS mice.[23]

Study limitations

Our study was subject to several limitations. First, our data might have been more reliable if we had been able to take sequential serum samples as the disease progressed. Second, this study was retrospective, and we could not obtain more detailed information about other nutritional assessments such as body impedance analysis for fat-free mass, indirect calorimetry, and determination of body mass index, individual resting energy expenditure, and vital capacity.[7] Third, we were unable to select the patients and control subjects at the same period of time. Fourth, the finding of a lack of difference between the basal serum lipid levels in female ALS patients and female controls could be confounded by the relatively small number of female patients.

Conclusion

Despite its limitations, the present study is important because it is (to our knowledge) the first to have assessed changes in serum metabolite levels in a large number of ALS patients in a well-controlled manner. The results show that increased metabolic demand may be observed in the early stages of the disease, and the pathophysiology of ALS may show gender-related differences. Further studies with a prospective design are required to determine the exact role and possible effect of gender on the increased metabolic demand in ALS.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Supplementary Table 1. Basal serum levels of lipids, proteins, and glucose in women with amyotrophic lateral sclerosis (ALS), and in sex-matched controls

	ALS (females)	Control (females)	*p*
n	35	35	
Age (years)	53.63±8.77	52.49±8.46	0.581
Cholesterol (mg/dL)	202.34±36.82	200.91±27.03	0.853
LDL (mg/dL)	125.34±31.40	120.51±21.62	0.456
HDL (mg/dL)	50.69±10.43	50.26±11.54	0.871
Triglycerides (mg/dL)	131.34±98.15	130.89±109.19	0.985
LDL/HDL ratio	2.56±0.79	2.24±0.96	0.122
Protein (g/dL)	7.19±0.44	7.28±0.30	0.300
Glucose (mg/dL)	94.52±20.12	91.69±8.34	0.444

Data presented as mean±standard deviation.
HDL: high-density lipoprotein, LDL: low-density lipoprotein, *n*: number.