Is hyperlipidemia correlated with longer survival in patients with amyotrophic lateral sclerosis?

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Amyotrophic lateral sclerosis (ALS) is the most serious form of degenerative motor neuron disease in adults, whose relentless course leads to death within 2–5 years, generally due to respiratory failure. Apart from the age and site of onset, no other factors have consistently demonstrated to be related to the ALS outcome. The aim of the study was to investigate the influence of fasting serum lipid levels (cholesterol and triglycerides) and the body mass index (BMI) at the time of diagnosis on survival in ALS patients. The study included 82 patients with ALS residing in the Belgrade area who were diagnosed with ALS over a time period of 4 years (2006–2009). Survival was assessed by the Kaplan–Meier method. In this retrospective study, 39 (47.56%) patients had normal values of lipids and 43 (52.43%) patients had hyperlipidemia. The mean survival time from the onset of symptoms for patients with normal lipidemia was 4.21 ± 0.5 years, while the mean survival time from the onset of symptoms for patients with hyperlipidemia was 5.0 ± 0.67 years (P=0.36). We also did not register a significant difference in survival in relation to gender, the site or age of onset, even though we noticed a longer survival in patients with hyperlipidemia in all of the examined groups, especially in the group of younger patients, with the onset of the disease before the age of 45 years. If we take into account the fact that BMI is pathophysiologically associated with cholesterol and triglyceride serum levels, the results in our study complement each other showing that patients with a higher BMI, registered in 28.8% of the cases, do not live longer. Our findings show that hyperlipidemia, which we found in 52.43% of our ALS patients, at the time of diagnosis, is not related to significantly longer survival.

Keywords: Amyotrophic lateral sclerosis, Hyperlipidemia, Survival, Body mass index

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that usually begins in the sixth or seventh decade of life and is characterized by upper and lower motor neuron degeneration. Death occurs, on average, in 50% of patients in the period between 2.5 and 3 years from the occurrence of symptoms due to respiratory paralysis.¹–³ About 25% of patients survive 5 years and around 5–10% of patients survive longer than 10 years.⁴

As most ALS patients have a very poor prognosis, increasing attention has recently been directed towards identifying the prognostic factors of longer survival. Moreover, it has been found that individual variability in survival time is considerable, thus making the planning of care and treatment even more difficult and costly.

Since Desport et al. registered that the patients with ALS and malnutrition had a shorter mean survival time, the lipid metabolism has been investigated more intensively, especially in the last ten years.¹⁰ Despite the findings of the existence of abnormal lipid metabolism in ALS, conflicting results have been reported about the role of hyperlipidemia and the body mass index (BMI), as possible factors for longer survival of ALS patients. Some authors consider hyperlipidemia as a significant prognostic factor in ALS,⁵–¹⁰ while others do not find hyperlipidemia to be significant in ALS patients.²,¹¹

The objective of this study is to correlate lipid levels and BMI with the survival time of ALS patients.

Patients and Methods

In this retrospective study, we investigated 82 patients with ALS whose data were taken from the central
database of the Neurology Clinic, Clinical Center of Serbia. *Access to data was approved by the Institutional Ethical Committee, according to the legal procedure prescribed.

All examined patients were residents of the Belgrade area, diagnosed between 2006 and 2009. Also, all patients met the revised El-Escorial criteria of probable or definitive ALS.12

Clinical data included age at onset, the site of onset (spinal or bulbar) and the survival time. Functional impairment due to ALS was evaluated using the ALS-Functional Rating Scale.

None of the patients in this group had a family history of ALS.

Non-invasively or invasively ventilated patients as well as patients with percutaneous endoscopic gastrostomy were excluded from the study. None of the examined patients used lipid lowering medications.

Laboratory tests included fasting serum levels of total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL), triglycerides and BMI at the time of diagnosis. For all patients, the blood samples were collected in the morning after a fasting period of 8–10 hours. The analysis of samples was done enzymatically with the Beckman Coulter® system.

Hyperlipidemia was defined as serum cholesterol level $>$ 5.20 mmol/l, HDL $<$ 1.60 mmol/l, LDL $>$ 3.40 mmol/l, and/or serum triglyceride level $>$ 1.70 mmol/l.

The BMI was defined as the ratio of weight in kilograms to height in meters squared ($\text{kg/m}^2$) using the World Health Organization criteria.

Each patient was regularly followed up during the disease.

Survival time was defined as the number of years that a patient with ALS survived, more specifically, the time from the onset of symptoms until the date of death from any cause. This information was recorded into the database as patients died. For persons who were still alive at the end of the study, the survival time was considered censored at that time.

All statistical analyses of the association between clinical manifestation and the survival pattern were analyzed using the SPSS 17.0 software.

The groups of ALS patients were formed for further analysis according to the following five criteria:

1. first criterion: two groups were formed in the following manner: Group 1 included all patients with hyperlipidemia and Group 2 included all patients with normal lipidemia;

2. second criterion: four groups were formed as follows: Group 1 included males with normal lipidemia, Group 2 included males with hyperlipidemia, Group 3 included females with normal lipidemia, and Group 4 included females with hyperlipidemia;

3. third criterion: four groups were formed in the following way: Group 1 included patients younger than 45 years with normal lipidemia, Group 2 included patients younger than 45 years with hyperlipidemia, Group 3 included patients older than 45 years with normal lipidemia, and Group 4 included patients older than 45 years with hyperlipidemia;

4. fourth criterion: four groups were formed as follows: Group 1 included patients with bulbar onset and normal lipidemia, Group 2 included patients with bulbar onset and hyperlipidemia, Group 3 included patients with spinal onset and normal lipidemia, and Group 4 included patients with spinal onset and hyperlipidemia;

5. fifth criterion: according to BMI, the patients were divided into five groups (using the World Health Organization criteria): Group 1 included underweight patients ($\text{BMI < 18.5}$), Group 2 included patients with a normal nutritional status ($18.5 \leq \text{BMI} < 24.9$), Group 3 included overweight patients ($25 \leq \text{BMI} < 29.9$), Group 4 included obese patients ($29.9 \leq \text{BMI} < 34.9$), and Group 5 included excessively obese patients ($\text{BMI} \geq 35$).

For each of the five criteria, there were between two and five groups of patients formed from the entire sample. The main goal was to find whether there was any difference in survival patterns between the groups, analyzed separately for each of the five criteria.

The estimate of survival patterns was performed by the Kaplan–Meier procedure, and the comparison of survival patterns between groups was performed by applying the log-rank test and their significance was reported. The $P$ value $< 0.05$ was considered to be statistically significant.

Also, associations between serum cholesterol and survival time and between triglyceride level and survival time were obtained by determining respective Pearson correlation coefficients.

**Results**

Out of our sample of 82 patients with ALS, spinal onset was registered in 52 (63.4%) patients, of which 24 (46.2%) males and 28 (53.8%) females.

Bulbar onset was recorded in 30 (36.6%) of our patients, 16 (53.3%) males, and 14 (46.7%) females.

The mean age at the onset of symptoms was 53.78 ± 11.53 years (range: 27–72 years). There were nine (11%) patients with the onset of disease before 45 years.

The mean duration of the disease at the time of investigations was 1.62 ± 0.10 years yielding a mean survival time of 4.19 ± 0.47 years. The mean ALS-Functional Rating Scale at time of diagnosis was 53.78 ± 11.53 years (range: 46–63 years).

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We did not find a statistically significant difference in the mean survival time between the bulbar and spinal onset of ALS patients according to the lipid status, as presented in Table 2 (log-rank test, $P=0.97$ for bulbar ALS onset and $P=0.72$ for spinal ALS onset). ALS patients with bulbar onset and normal lipidemia had the mean survival time of $2.67 \pm 0.25$ years, while for those with hyperlipidemia, it was $3.5 \pm 0.93$ years. ALS patients with spinal onset and normal lipidemia had a mean survival time of $4.10 \pm 0.57$ years, while for those with hyperlipidemia, it was $4.87 \pm 0.99$ years.

At the time of diagnosis, the body mass index was known for 59 patients. The mean BMI was $26.74 \pm 14.95$. According to the values of the body mass index, we categorized our patients into five groups (Table 3):

- overweight patients had the mean survival time of $3.6 \pm 2.07$ years;
- patients with a normal nutritional status had the mean survival time of $4.02 \pm 2.51$ years;
- overweight patients had the mean survival time of $3.48 \pm 3.36$ years;
- obese patients had the mean survival time of $3.08 \pm 1.56$ years;
- excessively obese patients had the mean survival time of $4.32 \pm 3.44$ years.

While the mean survival time for the patients with BMI $>35$ was the longest ($4.32 \pm 3.44$ years), we did not find a statistically significant difference between the groups (log-rank test, $P=0.91$).

We calculated the Pearson correlation coefficient between the mean survival time and the serum cholesterol ($R=-0.048$, $P=0.7$) and triglyceride ($R=-0.13$, $P=0.28$) levels, but determined no statistical significance.

**Discussion**

The results of our study showed that 52.4% of ALS patients had hyperlipidemia at the time of diagnosis, which was higher than the prevalence of hyperlipidemia in the general adult Serbian population (33.7%).

This result had to be interpreted with caution because there was no local control group and the epidemiological data used for comparison were not matched for age, gender, and other variables.

However, our results support the study of Dupuis et al. which registered a twofold higher total

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Table 1: Characteristics of patients with ALS and laboratory values

<table>
<thead>
<tr>
<th>Item</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>82</td>
</tr>
<tr>
<td>Mean age at onset (years)</td>
<td>$53.78 \pm 11.53$</td>
</tr>
<tr>
<td>Median diagnostic delay (years)</td>
<td>1.62 \pm 0.10</td>
</tr>
<tr>
<td>Male</td>
<td>41 (50.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (50.0%)</td>
</tr>
<tr>
<td>Spinal onset</td>
<td>52 (63.4%)</td>
</tr>
<tr>
<td>Bulbar onset</td>
<td>30 (36.6%)</td>
</tr>
<tr>
<td>&lt;45 years</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>&gt;45 years</td>
<td>73 (89%)</td>
</tr>
<tr>
<td>Mean survival time (years)*</td>
<td>4.19 \pm 0.47</td>
</tr>
<tr>
<td>Total cholesterol serum level (mmol/l)*</td>
<td>5.80 \pm 1.39</td>
</tr>
<tr>
<td>Triglyceride serum level (mmol/l)*</td>
<td>1.87 \pm 1.22</td>
</tr>
<tr>
<td>HDL-cholesterol serum level (mmol/l)*</td>
<td>1.37 \pm 0.81</td>
</tr>
<tr>
<td>LDL-cholesterol serum level (mmol/l)*</td>
<td>2.95 \pm 1.01</td>
</tr>
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Note: *Mean level $\pm$ SD.

In the present study, 39 (47.56%) patients had normal lipidemia in comparison with 43 (52.43%) patients with hyperlipidemia (Table 2).

The mean survival time was 4.21 $\pm 0.5$ years for patients with normal lipidemia and 5.0 $\pm 0.67$ years for patients with hyperlipidemia.

Although we observed that there was a small difference between these groups as to the mean survival time, we did not find this difference to be statistically significant (log-rank test, $P=0.36$).

According to gender, we registered a mean survival time of 4.22 $\pm 0.66$ years, for males with normal lipidemia and 5.4 $\pm 1.39$ years for males with hyperlipidemia.

The mean survival time for females with normal lipidemia was 4.02 $\pm 0.75$ and 4.6 $\pm 0.61$ years for females with hyperlipidemia (Table 2). We did not find a statistically significant difference between them (log-rank test, $P=0.40$).

According to the age, for patients younger than 45 years with normal lipidemia, the mean survival time was 2.63 $\pm 0.62$ years, while for those with hyperlipidemia, it was 6.9 $\pm 2.01$ years. Patients older than 45 years with normal lipidemia had a mean survival time of 4.26 $\pm 0.52$ years and those with hyperlipidemia of 4.28 $\pm 0.54$ years (Table 2). We did not register a statistically significant difference between them (log-rank test, $P=0.67$).

Table 2: The mean survival time for different groups of ALS patients

<table>
<thead>
<tr>
<th>Group of patients</th>
<th>Group of patients with normal lipidemia</th>
<th>Group of patients with hyperlipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean survival time</td>
<td>4.21 $\pm 0.5$ years</td>
<td>5.0 $\pm 0.67$ years</td>
</tr>
<tr>
<td>Male</td>
<td>4.22 $\pm 0.66$ years</td>
<td>5.4 $\pm 1.39$ years</td>
</tr>
<tr>
<td>Female</td>
<td>4.02 $\pm 0.75$ years</td>
<td>4.6 $\pm 0.61$ years</td>
</tr>
<tr>
<td>&lt;45 years</td>
<td>2.65 $\pm 0.62$ years</td>
<td>6.9 $\pm 2.01$ years</td>
</tr>
<tr>
<td>&gt;45 years</td>
<td>4.26 $\pm 0.52$ years</td>
<td>4.28 $\pm 0.54$ years</td>
</tr>
<tr>
<td>Bulbar onset</td>
<td>2.67 $\pm 0.25$ years</td>
<td>3.5 $\pm 0.93$ years</td>
</tr>
<tr>
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<td>4.10 $\pm 0.57$ years</td>
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</table>
cholesterol level and LDL plasma level, in comparison to the controls, and the study of Dorst et al. which evidenced hypertriglyceridemia in more than one-third of ALS patients.

Although we found that around half of our patients had hyperlipidemia, when we compared the mean fasting plasma levels of cholesterol, triglycerides, and HDL and LDL according to gender, type, and age at onset, we did not find a significant difference among them.

Our patients with hyperlipidemia lived a little longer in comparison to the patients with normal lipidaemia, but this difference was not statistically significant. Our findings are therefore not consistent with the findings of Dorst et al. and Depuis et al. who considered hyperlipidemia as a significant prognostic factor for survival of patients with ALS.

We also did not register a statistically significant difference in survival time in relation to gender, the site, or age of onset even though we noted a longer survival time in patients with hyperlipidemia in all of the examined groups, especially in the group of younger patients, with the onset of the disease before the age of 45 years.

Finally, we did not register any significant correlation between the mean survival time and the serum cholesterol and triglyceride levels in our group of patients.

Our results support the study by Chio et al. who did not find hyperlipidemia to be related to longer survival, although they also failed to register a difference between the fasting lipid status in ALS patients and the controls. Also Sutedja et al. did not find that vascular risk factors, measured clinically and biochemically, were associated with increased ALS.

The causes of hyperlipidemia in patients with ALS, detected in recent studies, are unclear. Hyperlipidemia has been offered as a possible explanation of energy imbalance in ALS. Sutedja et al. consider that a higher metabolic rate plays a role in ALS.

Kim et al. found hypolipidemia in the presymptomatic stage of the ALS mouse model, in the absence of malnutrition, and in the absence of significant neuromuscular degeneration and respiratory difficulty. Their findings suggest that hypolipidemia in ALS is not an epiphenomenon of neuromuscular degeneration, respiratory difficulty, or energy imbalance but a lipid-specific metabolic deterioration.

If we take into account that BMI is pathophysiologically associated with cholesterol and triglyceride serum levels, the results in our study complement each other showing that patients with a higher BMI, registered in 28.8% of the cases, do not live longer.

We know that this study had some limitations, such as a relatively small number of patients and the absence of a control group, but this study seems to support previously reported findings that have not find a link between the lipid metabolism of ALS patients and their longer survival.

**Conclusion**

The results of this study show that hyperlipidemia, which we found in half of our ALS patients, was not related to significantly longer survival. This was the first study performed in Serbia to examine the impact of lipid metabolism on the survival of patients with ALS.

A future study with a larger sample also designed to include a control group, would provide more detailed information. We will certainly continue to carefully plan the therapeutic strategy related to adequate nutrition and the use of statins in ALS patients.

**References**


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**Table 3 The mean survival time of ALS patients according to BMI**

<table>
<thead>
<tr>
<th>Group of patients</th>
<th>Number of patients (n=59)</th>
<th>Mean survival ± SD (years)</th>
</tr>
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<tbody>
<tr>
<td>Underweight</td>
<td>5 (8.5%)</td>
<td>3.6 ± 2.07</td>
</tr>
<tr>
<td>BMI &lt;18.5</td>
<td>27 (45.7%)</td>
<td>4.02 ± 2.51</td>
</tr>
<tr>
<td>Normal nutritional status</td>
<td>17 (28.8%)</td>
<td>3.48 ± 3.36</td>
</tr>
<tr>
<td>Overweight</td>
<td>6 (10.2%)</td>
<td>3.08 ± 1.56</td>
</tr>
<tr>
<td>BMI: 25–30</td>
<td>4 (6.8%)</td>
<td>4.32 ± 3.44</td>
</tr>
<tr>
<td>Obese</td>
<td></td>
<td></td>
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<tr>
<td>BMI: 30–35</td>
<td></td>
<td></td>
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<tr>
<td>Excessively obese</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &gt;35</td>
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