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Gender and Age Differences in Lifestyle Factors and Risk of Amyotrophic Lateral Sclerosis; A Case-Control Study in Japan

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Abstract

Background: We examined associations between lifestyle factors and the risk of ALS by combination of gender and age group (<65 year vs. ≥65 years), using a population-based case-control study in Japan.

Methods: The study comprised 183 ALS patients diagnosed by El Escorial World Federation of Neurology criteria, and 306 genders- and age-matched controls randomly selected from the general population using the basic register of residents. Detailed information on lifestyle factors was obtained through a mailed self-administered questionnaire. The strength of association between ALS and a potential risk factor was assessed by calculating Odds Ratios (ORs) and 95% Confidence Intervals (CIs).

Results: Type A behavior pattern was significantly associated with an increased ALS risk in all combination of gender and age group, and frequent intake of green-yellow vegetable was associated with an increased ALS risk in combination of gender and age group other than men ≥65 years. Moreover, vigorous exercise was associated with an increased ALS risk among men aged <65 years, and self-reported stress in both men and women aged ≥65 years.

Conclusion: The present study found that Type A behavior pattern was associated with an increased ALS risk in all combination of gender and age group (<65 year vs. ≥65 years), the lifestyle factors were observed significant association only specific in combination of gender and age group. These findings suggest that Type A behavior as patient-specific endogenous oxidative stress may increase the risk of ALS common in all combination of gender and age group.

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease of unclear etiology involving spinal cord motor neurons, leading to atrophy of skeletal muscles, paralysis and rapidly-progressive death. The majority of the patients are sporadic cases (SALS), while 5-10% of the patients have a family history of ALS (familial ALS or FALS) [1]. It is considered that ALS is a multifactorial disease in which complex environmental and genetic factors interact. Most studies have focused largely on heavy physical activity, skeletal fracture and heavy metal exposure at work [2-8]. We have already found that imbalance between excessive productions of endogenous oxidative stress such as Type A behavior pattern and the decrease or lack of antioxidant defense in brain nerves such as less frequent intake of green-yellow vegetables may increase the risk of ALS for both gender combined [9,10]. However, it is speculated that risk factors of ALS are not already common to all participants and are different in the characteristic such as gender and age groups. It leads to make preventive measures for the primary prevention of ALS for targeting individuals/populations such as gender and age groups. To the best of our knowledge, however, no epidemiological studies have examined that relationship between lifestyle factors and ALS risk by gender and age. We, therefore, conducted a case-control study to explore the association of lifestyle factors with the risk of ALS by gender and age, using a relatively large number of patients in Japan.

Materials and Methods

Study subjects and method were previously described in detail [9]. Briefly, the study population included patients with newly diagnosed ALS enrolled in population-based registries in the medical centers located in the Tokai area in Japan from January 2000 through December 2004. Patients were included if they were aged from 18 to 81 years and had definite, probable ALS according to the El Escorial (EE) diagnostic classification by at least one neurologist [11].

To be eligible as cases for the present study, patients had to have diagnosed as ALS within 3 years at the time of study and to be 18 to 81 years old. ALS was definite in 65% and probable in 35%. All cases of Progressive Bulbar Palsy (PBP) were included for this study, but individuals with neurodegenerative disorders (Alzheimer's and Parkinson's disease, Huntington's chorea); patients in whom hospital admission was related to trauma or orthopedic/surgical illnesses and familial progressive muscular atrophy were excluded. There was no evidence of coexisting Parkinson disease and related disorders including multisystem atrophy. To facilitate the recall of lifestyles, including dietary habits, we inserted into the questionnaire some questions about their familial and social backgrounds at that time. The present study was approved by the institutional review board of Aichi Prefectural College of Nursing & Health.

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We set up two community controls matched to each patient for age (±2 years), gender and residence based on electoral districts. They were selected by a proportional simple random sampling from among general population in the same district as our case subjects with stratification by sex and age group.

A structured self-administered questionnaire specifically designed for this case-control study was distributed and collected by mail in both patients and controls. We asked patients to recall their lifestyle within the 3 years before the onset of ALS, and controls within the 3 years before the survey.

The questionnaire yielded information on demographic characteristics sex, age, height, and present and past weight, occupation and work environment held the longest, a history of bone fracture, vigorous physical activity, hate to lose, self-reported stress, Type A behavior pattern, smoking and drinking habits, physical stiffness by nature, and frequency of green-vegetable intake.

Participants were asked to recall whether they had been performed vigorous physical activity which made you sweat or get out of breath more than three times per week in leisure time. Type A behavior pattern was measured by ten-item scale designed for Japanese persons by Maeda [12]. Subjects who scored between 0 and 16 considered as non-type A, while those who scored 17 or greater were considered as type A. Participants were asked to report their self-reported psychological stress intensity as "never/hardly" or, if stressed,"light", "moderate" or "high". Subjects who responded "moderate" or "high" were considered to be "high", and those who responded "never/hardly" or "light" were considered to be "low". Smoking status was classified as current smokers or nonsmokers (including ex-smokers). Drinking status was classified as current drinkers or nondrinkers (including ex-drinkers). Subjects were asked intake frequencies of green-yellow vegetables with five response options as follows: "never/seldom,""less than once a week," "1-2 times per week," "3-4 times per week," and "almost everyday," and the frequency was dichotomized as "frequent" ("3-4 times per week"/"almost everyday") *vs.* "less frequent" ("never/seldom"/"less than once a week"/"1-2 times per week").

Estimation of Odds Ratios (ORs) and their 95% Confidence Intervals (CIs) were carried out by means of multiple conditional logistic regression analysis. Tests for trend in logistic regression analysis was performed by the exposure variables and treating the scored variables as a continuous one. Two-sided p values less than 0.05 were considered statistically significant. Statistical analyses were conducted by use of SPSS ver24.0 (SPSS Japan Inc) was used.

Results

214 (75.3%) eligible cases among 274 patients aged from 18 to 81 years who met the criteria, and 550 (75.2%) among 732 eligible community controls were enrolled. Among them, 183 patients and 407 community controls were completed the entire questionnaire and agreed to participate in the case-control study. As shown in Table 1, no significant difference in mean age and proportion of men was found between cases and controls. As shown in Table 2, Type A behavior pattern was significantly associated with an increased ALS risk in all combination of gender and age group (<65 year *vs.* ≥65 years), but less frequent intake of green vegetables had a significant association except for men aged ≥65years. Moreover, vigorous exercise among men aged <65 years and self-reported stress in both men and women aged ≥65years were associated with an increased ALS risk.

Table 1: Comparison of selected characteristics of cases and controls.

	Cases (n=183)	Controls (n=407)	*p* for trend
	% or Mean	% or Mean	
Men (%)	60.8	59.1	
Mean age (SD)	63.7±9.2	63.4±10.6	*N.S*
Use of proxy respondents (%)	67.5	67.5	*N.S*
Body Mass Index (BMI)	22.2±0.2	23.3±0.3	*p*=0.04
Type A behavior pattern (%)	44.2	19.6	*p*=0.000
Smoking habit (%)	58.1	54.1	*N.S*
Drinking habit (%)	35.3	31.4	*N.S.*

Discussion

In this case-control study, we found that Type A behavior pattern as oxidative stress were strongly associated with an increased risk of ALS common in all combination of gender and age group (<65 year *vs.* ≥65 years), and specific lifestyle factors associated with an increased risk of ALS in each combination alone. This is the first case-control study to explore common risk factors in all combination of gender and age group and specific risk factors by each combination of gender and age group. A methodological issue was analyzed for sporadic and familial ALS combined. Cu/Zn Superoxide Dismutase (SOD1) gene is associated with an unusual, slowly-progressing form of Familial Amyotrophic Lateral Sclerosis (FALS) and is less frequent in sporadic ALS cases (2.6 %) [13]. In this study, we had also the small proportion of subjects with positive familial ALS (1.9%). These findings imply that the sporadic and familial forms of ALS are clinically and pathologically indistinguishable. Moreover, we used self-administered questionnaire to obtain retrospectively information. Therefore, the reliability of self-administered questionnaire was assessed using the test-retest over a two week period for fifty persons randomly selected among community controls. Kappa values ranged from a low of 0.52 for general stress to a high of 0.86 for smoking habit, suggesting that the measures in this study might be considered adequately reliable.

We previously reported that the greatest effect on risk for ALS was the combination of Type A behavior pattern and less frequent intake of green-yellow vegetables [9]. According to the analysis by combination of gender and age group, however, only Type A behavior pattern had significant association with increased risk of ALS common in all combination of gender and age group. What we examined the risk factors according to combination of gender and age group, it was because it was necessary and important to make a more practical and concrete preventive strategy considered the differences in the characteristic of total subjects such as combination of gender and age group, although it was also necessary to define an overall trend of risk factors for all subjects to make a strategy as initial preventive measure. Significant relationship between Type A behavior pattern and an increased risk of ALS was commonly observed in all subgroups by gender and age groups.

It is known that the Type A personality has being impatient, excessively time-conscious, insecure about one's status, highly

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Table 2: ORs according to lifestyle factors by combination of gender and age group.

	Men		Women	
	<65 years	65 years	<65 years	65 years
Bone fracture	1.67 (0.89-3.07)	1.41 (0.72-2.75)	0.92 (0.31-2.78)	1.74 (0.70-4.34)
Heavy exercise	3.37 (1.43-7.49)	1.33 (0.61-2.91)	0.51 (0.05-4.86)	2.95 (0.47-18.7)
Type A behavior	3.47 (2.15-6.51)	1.78 (1.05-3.02)	3.20 (1.59-6.44)	1.95 (1.02-3.86)
Hesitate to lose	2.11 (1.24-3.61)	0.79 (0.44-1.41)	1.52 (0.78-2.95)	1.55 (0.81-2.99)
Self-reported stress	1.58 (0.91-2.71)	2.13 (1.25-3.63)	1.39 (0.72-2.68)	2.54(1.29-5.01)
Smoking habit	0.85 (0.45-1.59)	0.93 (0.52-1.65)	1.25 (0.59-2.67)	1.38 (0.45-4.27)
Drinking habit	2.06 (1.19-3.59)	1.18 (0.70-1.96)	0.61 (0.28-1.32)	0.96 (0.33-2.78)
Less frequent intake of green-yellow vegetable	3.52 (2.02-6.12)	1.10 (0.92-3.68)	3.86 (1.80-8.29)	3.16 (1.42-7.05)

competitive, hostile and aggressive, and incapable of relaxation. Moreover, Type A individuals are often highly achieving workaholics who multi-task, drive themselves with deadlines and are unhappy about the smallest of delays. Dissatisfaction and stress were related to more frequent symptom complaints in the Type As [14].The relations between role conflict and physical strain and between role conflict and psychological strain were significantly positive and higher among Type A personalities than among Type B Personalities [15].

The stress symptoms of Type As were significantly predicted by the insufficient use of effective coping styles and deficiencies in the general mood component of emotional intelligence [16].

Considering the above-mentioned the characteristic of the behavior, it is highly likely that Type A behavior pattern being stress-producing behavior affect enhanced oxidation of nerve as endogenous oxidative stress [17-20].

It appears that the stress has continuously been generated from innate character and unchangeable behavior, and influenced motor neuron. Moreover, we also observed that vigorous exercise as chronic physical stress among men aged <65 years and self-reported stress as psychological stress in men and women aged ≥65 years, implying that factors significantly associated with the risk of ALS are different in each of subgroup alone. Therefore, our findings indicate that it is essential to consider those simultaneously, when making preventive measures for primary prevention of ALS by subgroup of gender and age, not separately.

There are several limitations to this study. First, we used prevalent patients whose diagnosis was made within 1-4 years before the present study, which would result in some difficulty in recalling their conditions before the onset of ALS. It is quite likely that prevalent cases often take the influence of the recall bias in comparison with incident cases. In this study, the association of the studied variables and the risk of ALS remained even after we reanalyzed for the subjects within one year before the onset of ALS, although the number of cases were small (n=64). Second, our questionnaire asked several information 3 years before recruitment into study. This is because we examine the causality between lifestyle factors before the onset of ALS and the risk of one. Accordingly, the possibility could arise that lifestyle exposure might have occurred after initiation of ALS development. Therefore, we have confirmed that all of cases had no significant change in their lifestyle between at 3 years and 10 years prior to disease onset. To avoid these problems, we are now planning relatively large population- based prospective study. Third, we used self-administered questionnaire to collect information in both cases and controls. The authors have demonstrated no significant difference in the responses to questions related to lifestyle factors such as physical activity, general life stress and dietary habit between self- and interviewer-administered questionnaires [21]. The relationship between vigorous physical activity and the risk of ALS in this study was like previous studies conducted by interviewer-administered questionnaires [2-4]. These findings suggest that the effect of collection method on the responses might be would be minimal.

The present study found that Type A behavior pattern was associated with an increased ALS risk in all combination of gender and age group (<65 year *vs.* ≥65 years), but the lifestyle factors were observed significant association only specific in combination of gender and age group. These findings suggest that Type A behavior as patient-specific endogenous oxidative stress may increase the risk of ALS common in all combination of gender and age group.

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