Brief Original Contribution

Early-Onset Alopecia and Amyotrophic Lateral Sclerosis: A Cohort Study

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Abbreviation: ALS, amyotrophic lateral sclerosis.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with a median survival of 1.5–3 years after diagnosis (1). The lifetime risk of ALS ranges from 1 in 1,000 to 1 in 400 according to different estimates (2, 3). The cause of ALS is largely unknown, and there is no effective treatment to date. Several observations suggest a link between early balding (alopecia) and ALS. ALS affects all motor neurons and cranial nerves except those that lack androgen receptors (4); a repeat expansion in the androgen receptor gene causes spinobulbar muscular atrophy (5), a nonfatal motor neuron disease similar to ALS, but does not cause ALS (6). Other mutations in the androgen receptor gene and increased sensitivity of the androgen receptor are linked to alopecia (7, 8). Furthermore, in a recent meta-analysis of 7 European genome-wide association studies, a single nucleotide polymorphism in the area of the ALS gene TAR DNA-binding protein 43 (*TARDBP/TDP-43*) (9) was linked to alopecia. No previous studies have directly examined the association between alopecia and ALS. We therefore explored the association between early-onset alopecia and ALS among participants in a large cohort of US men.

MATERIALS AND METHODS

Study population

The Health Professionals Follow-up Study is a longitudinal study of 51,529 male health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians), aged 40–75 years at enrollment, who completed a mailed questionnaire about lifestyle and medical history in 1986 and similar biennial questionnaires since then (10).

Alopecia assessment

In 1992, participants reported their balding status at age 45 years by choosing from 5 crown-view pictograms based on Norwood's classification of male-pattern baldness (Norwood's I, III, IV, V, and VII) (11) (Figure 1). The original 5-category classification of alopecia was collapsed into 3 categories as follows: no alopecia (Norwood's I), moderate alopecia (Norwood's III or IV), and extensive alopecia (Norwood's V or
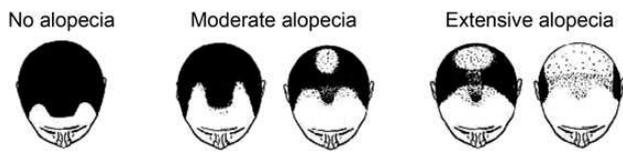
Figure 1.   Pictograms used to assess level of balding in the Health Professionals Follow-up Study in 1992. Pictograms are based on Norwood's classification of male-pattern baldness. (No alopecia = Norwood's I; moderate alopecia = Norwood's III or IV; and extensive alopecia = Norwood's V or VII). This figure is reproduced from Norwood (11), with permission from Wolters Kluwer Health, copyright 1975.

VII) for analysis purposes. This study was approved by the human subjects committee at the Harvard School of Public Health (Boston, Massachusetts).

Ascertainment of ALS

In each biennial follow-up questionnaire, participants were asked to report a specific list of medically diagnosed conditions and "any other major illness." ALS was added to the list of specific conditions beginning in 2000. We requested permission to contact the treating neurologists for release of relevant medical records from participants who reported a diagnosis of ALS on the open question on major illnesses or on the specific question about ALS. Because of the rapidly progressive nature of the disease (median survival, 1.5–3 years) (1), many participants with ALS died before we could send the request for release of medical records, so the request was sent to the closest family members. After obtaining permission, we asked the treating neurologists to complete a questionnaire to confirm the diagnosis of ALS and to rate the certainty of the diagnosis (definite, probable, or possible) and send medical records. Starting in 2004, the questionnaire was modified to include the El Escorial diagnostic criteria (12). The final confirmation for our study purposes was made by a neurologist with experience in ALS diagnosis on the basis of the review of medical records. We relied on the diagnosis made by the treating neurologist if the information in the medical record was insufficient or if it could not be obtained. Only participants with definite or probable ALS were included as cases. When we were unable to confirm (i.e., obtain a copy of the medical record or the neurologist's questionnaire) incident self-reported ALS, we classified the participant as having "possible ALS" and excluded him from the analysis unless death occurred during follow-up and ALS was listed on the death certificate.

Vital status of the participants was determined by automated linkage with the National Death Index. The underlying and contributing causes of death were coded according to the *International Classification of Diseases, Ninth Revision*. All individuals with code 335.2 (motor neuron disease) listed as the underlying or contributing cause of death were considered to have had ALS. In a previous validation study (13), it was found that ALS was the primary diagnosis listed

on death certificates in the majority of instances in which code 335.2 was listed as a cause or contributory cause of death (13).

Data analysis

Person-time was calculated from the date of return of the 1992 questionnaire until the date of first onset of ALS symptoms (37 cases), death from ALS or any other cause (5 cases), or the end of follow-up (December 31, 2008). Cox proportional hazards regression was used to estimate relative risks and 95% confidence intervals for different stages of alopecia in relationship to ALS. We stratified the Cox models by age in single years to obtain better age adjustment.

There are few established risk factors for either alopecia or ALS. Smoking has been suggested to increase the risk of ALS (14), as well as alopecia (15). High premorbid body mass index (weight (kg)/height (m)^2) (16) and vitamin E intake (17) have been reported to be associated with a lower ALS risk. However, these variables are not known to be associated with alopecia and were therefore included in secondary analysis only. In a subanalysis, we excluded users of finasteride, a drug that blocks dihydrotestosterone production and that is used to treat enlarged prostate and alopecia; in this subanalysis, we used as baseline the date of return of the 1996 questionnaire, which was the first to inquire about finasteride use.

In total, we identified 42 cases of ALS in 565,125 person-years contributed by 40,046 men. Analyses were performed by using SAS, version 9.2, software (SAS Institute Inc., Cary, North Carolina).

RESULTS

The distribution of baseline characteristics was similar across alopecia groups (Table 1). Of the 42 participants diagnosed with ALS during the follow-up period, 13 reported no alopecia at age 45 years, 18 reported moderate alopecia, and 11 reported extensive alopecia (Table 2). The crude incidence rate of ALS increased with age as follows: below 60 years, 1.3 cases/100,000 person-years; 60–70 years, 3.0 cases/100,000 person-years; and 70 years or older, 7.1 cases/100,000 person-years. Participants reporting extensive alopecia had an almost 3-fold increased risk of ALS compared with those reporting no alopecia (relative risk adjusted for age and smoking = 2.74, 95% confidence interval: 1.23, 6.13). When additional adjustments were made for body mass index and vitamin E intake, results were similar (relative risk = 2.75, 95% confidence interval: 1.23, 6.15). Further, we observed a significant linear trend across increasing levels of balding at age 45 years and risk of ALS ($P_{trend} = 0.02$) (Table 2). When we used 5 alopecia categories instead of 3, the results were similar (P for linear trend = 0.03). To avoid the potential influence of alopecia-associated drug use, we excluded finasteride users in a secondary analysis (2 cases among 716 users). In this analysis (which required moving the baseline from 1992 to 1996, when finasteride use was first assessed), the multivariable adjusted relative risk of ALS comparing extensive alopecia with no alopecia was 2.85 (95% confidence interval: 1.10, 7.41). Approximately 95% of participants in the Health Professionals Follow-up Study are of Caucasian descent. We

Table 1. Age-Standardized Characteristics of Study Participants at Baseline According to Level of Balding at Age 45 Years in the Health Professionals Follow-up Study, 1992–2008

Baseline Characteristic	No Alopecia (n = 17,568 men)		Moderate Alopecia (n = 16,980 men)		Extensive Alopecia (n = 5,498 men)	
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Participants	43.9		42.4		13.7	
Age in 1992, years		60.1 (9.6)		60.1 (9.7)		60.7 (9.9)
Body mass index[a,b]		25.4 (3.2)		25.4 (3.1)		25.7 (3.4)
Current smoker[b]	9.7		9.0		7.8	
Vitamin E supplement use[b]	21.2		20.8		19.8	

Abbreviation: SD, standard deviation.
[a] Calculated as weight (kg)/height (m)^2.
[b] Age-standardized value.

therefore performed additional analysis excluding all non-Caucasian participants (1 ALS case), but the results remained similar to the main results (relative risk = 2.44, 95% confidence interval: 1.07, 5.58).

DISCUSSION

In this large cohort of male health professionals, self-reported early-onset alopecia was associated with a higher risk of ALS. Our study benefits from prospective case ascertainment and thereby includes both slow-progressing and fast-progressing cases. Alopecia at age 45 years was self-reported retrospectively by participants aged 46–81 years; however, because participants did not have ALS at the time of exposure assessment, any differences in reporting are likely nondifferential with respect to ALS.

In this study, information on alopecia was available at age 45 years only. Further information on changes of alopecia status over time, especially alopecia assessment at an earlier age, would be of value in future studies. An important limitation of this study is the low number of ALS cases (n = 42). The results of this study should be interpreted with caution, and the hypothesis of alopecia and its association with ALS should be tested in other populations. Another limitation is that we were unable to study the risk of alopecia and ALS in different ethnic and racial groups, and further studies should be conducted to explore this association. As in all observational studies, there might be unmeasured confounding by unknown predictors of ALS.

Our results are consistent with the involvement of androgens in the etiology of ALS, a hypothesis that has been proposed previously (4, 18–20). A possible link between alopecia and ALS is the *TARDB/PTDP-43* gene. In a recent meta-analysis of 7 genome-wide association studies including more than 12,800 individuals of European ancestry, a single nucleotide polymorphism (rs12565727) in the area of the ALS gene *TARDB/TDP-43* was linked to alopecia (9). This single nucleotide polymorphism was not found to be in high linkage disequilibrium (defined as $R^2 > 0.8$) with genetic variants within *TARDBP/TDP-43*. Linkage disequilibrium was evaluated by single nucleotide polymorphism annotation and proxy search (21). However, given their physical proximity, it is still possible for rs12565727 to influence *TARDBP/TDP-43* through functional regulatory mechanisms. The *TARDBP/TDP-43* gene codes for the TDP-43 protein and is involved in regulating gene expression and RNA splicing (22). Even though mutations in the *TARDBP/TDP-43* gene are reported in only about 2%–5% of ALS cases (23), TDP-43–dominant protein aggregates are found in dying motor neurons in about 95% of ALS cases (22, 24, 25).

Table 2. Relative Risk of Amyotrophic Lateral Sclerosis by Level of Balding in Men in the Health Professionals Follow-up Study, 1992–2008

Level of Balding	No. of ALS Cases	Age-Adjusted Relative Risk	95% CI	Multivariate Relative Risk[a]	95% CI	Multivariate Relative Risk[b]	95% CI
No alopecia	13	1.00	Referent	1.00	Referent	1.00	Referent
Moderate alopecia	18	1.45	0.71, 2.97	1.47	0.72, 2.99	1.44	0.71, 2.95
Extensive alopecia	11	2.69	1.20, 6.01	2.74	1.23, 6.13	2.75	1.23, 6.15
P_{trend}		0.020		0.018		0.018	

Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval.
[a] Adjusted for age (in single years) and smoking status (current, previous, or never).
[b] Adjusted for age (in single years), smoking status (current, previous, or never), body mass index (weight (kg)/height (m)^2) (in categories of underweight, normal, overweight, and obese), and vitamin E supplement use (yes or no).

Neither the cause of ALS nor the cause of alopecia is fully understood. Although the presence of dihydrotestosterone is required for the development of alopecia (8), circulating levels of dihydrotestosterone have not been shown to be associated with alopecia. Rather, it is the sensitivity of androgen receptors, pairing with dihydrotestosterone in hair follicles, that is thought to be the cause (8). This process is regulated by several coactivators and corepressors (8). We speculate that androgen receptor sensitivity might play a role in ALS etiology as well, possibly with the involvement of TDP-43 protein abnormalities. In conclusion, we found an association between early-onset alopecia and ALS. The mechanisms underlying this association deserve further investigation.

ACKNOWLEDGMENTS

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