Potential Environmental Factors in Amyotrophic Lateral Sclerosis

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KEYWORDS

• ALS • Epidemiology • Environmental risk factors • Smoking • Gender • Military service • Oxidative stress

KEY POINTS

- Proven risk factors for ALS are genetic variants, male gender, and advanced age.
- The only environmental factor that is generally accepted to be associated with ALS is smoking.
- Some evidence supports US military service, lead exposure, physical activity, β-N-methylamino-L-alanine (BMAA), head trauma, electromagnetic fields, agricultural chemicals, and heavy metals as possible factors.
- ALS/Parkinson-dementia complex of Guam and the western Pacific is a distinct clinicopathologic entity; its cause may be different from ALS.
- Oxidative stress is a plausible mechanism through which many environmental risk factors may affect ALS.

INTRODUCTION

The causes of amyotrophic lateral sclerosis (ALS) are unknown for most patients. ALS is a clinically defined syndrome where upper and lower motor neurons degenerate, but

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it is not clear that the pathogenesis is identical across individual cases. It has been suggested that, for all cases, multiple events need to occur or multiple factors need to be present for the disease to manifest. Presumably these would include genetic susceptibility factors and the environmental or random factors that influence them. As of yet there are not any specific environmental factors that are proven to cause ALS, apart from smoking, but this article discusses several factors that have been examined, and their possible mechanisms. We summarize these in the table (**Table 1**) and rate of the strength of the association using the grading system proposed by Armon. Many proposed factors are not covered because there are more than 1000 epidemiologic ALS studies published. Controversy exists in regards to each of these factors ranging from limited data to conflicting evidence.

GENE-ENVIRONMENT INTERACTION

No gene conferring susceptibility to a certain environmental exposure has been established in ALS, but the search continues.[1] Several candidate ALS risk genes have emerged from association studies, but these results have not been replicable in other populations outside of where they were identified. Theoretically this could

Table 1
Proposed Risk factors for ALS

Proposed Risk Factor	Level of Increased Risk	Strength[62] and Type of Evidence	Proposed Mechanisms	References
Male gender	OR, 1.5	Level A	Early testosterone exposure	4
Smoking	OR, 1.1	Level A	Oxidative stress Lead Other toxins	63
US military service	OR, 0.22 to SMR, 1.92	Level B	Multiple	29
Lead	OR, 1.81	Level B	Neurotoxicity	42
Pesticides	OR Men, 1.88 Women, 1.31	Level B	Neurotoxic	51
Physical activity (or predilection thereof)	Unknown	Level U	Physical fitness, early testosterone exposure	43,44
Head trauma	Unknown	Level U	Direct neuronal injury	64
Electromagnetic radiation	Unknown	Level U	Electromagnetic field	37
Low body mass index	Unknown	Level U	Higher metabolism	45
Statin treatment	Unknown	Level U	Altered lipid metabolism	47
BMAA	Unknown	Level U	Neurotoxicity	17,18

Abbreviations: BMAA, β-*N*-methylamino-L-alanine; OR, odds ratio; SMR, standardized morbidity/mortality ratio.

Level A rating: This is an established risk factor, Level B rating: This is a probable risk factor ('more likely than not'), Level C rating: This is a possible risk factor (does not attain a 'more likely than not' status). Better-designed studies may be warranted with regard to this risk factor, Level U rating: It is unknown whether this is a risk factor.