Occupational causes of amyotrophic lateral sclerosis: where to from here?

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In a previous editorial in this journal[1] we have argued that there are likely to be important occupational causes of neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) (also commonly known as motor neuron disease) which have not yet been discovered or established.

However, for most neurodegenerative diseases, including ALS, the epidemiology has not been 'done', and there have been relatively few high-quality studies, in contrast to the situation with other non-communicable diseases (NCDs) such as cancer and respiratory disease.

Nevertheless, a number of occupational exposures are suspected of contributing to the risk of ALS,[2] including agricultural chemicals, metals, welding fume, electric shocks and extremely low-frequency electromagnetic fields (ELF-EMFs)[3] and organic solvents (eg, formaldehyde), although the evidence to date is inconsistent. Recently, a cluster of motor neurone disease (MND) cases has been linked to exposure to the fumigant methyl bromide.[4] Other putative risk factors include military service,[5] rural or urban residence, and a history of head injury including sporting injuries.[6 7]

The paper by Peters *et al*[8] in this issue of the journal is therefore potentially of considerable interest. It involves a case–control study conducted in Sweden during 1991–2010 which used the Nordic Occupational Cancer Study job-exposure matrix (NOCCA-JEM) to identify exposures related to individual occupations. The authors published results for exposure to electric shocks and extremely low-frequency magnetic fields for the same population and the same health outcome recently.[9]

The authors claim that theirs was the first study to apply a job-exposure matrix (JEM) to these issues, but in fact more than 10 years ago Parks *et al*[10] used several JEMs to assign occupational exposure in a large mortality study in 22 states in the USA, which included analyses of the risk for ALS and other neurodegenerative diseases. Nevertheless, the Swedish study is large (5020 cases and 25 100 controls) and population-based, and therefore might have been expected to make an important contribution.

However, the findings appear to be relatively limited, at least with regards to the new risk-factor findings that are reported in the current paper. The only positive associations (when assessed in terms of statistical significance) were for precision tool manufacturing and glass, pottery and tile work; there was a negative association with textile work. None of the occupational exposures for which the findings were reported were associated with ALS risk overall, although when the analysis was restricted to participants younger than 65 years, there was a weak positive association with formaldehyde, and a negative association with methylene chloride.

However, despite the large size of this study, which is most likely larger than all previous relevant case–control studies combined, there are a number of reasons why we should be cautious before concluding that occupational exposures are not important in the causation of ALS.

First, as noted above, this is not the first publication from this database, and the authors have previously reported findings regarding possible positive associations with exposure to electrical shocks and extremely low-frequency magnetic fields and ALS.[9] Furthermore, they have previously reported a significantly increased risk for welders <65 years (OR 1.52 (95% CI 1.05 to 2.21)) from the same database.

Second, there are also no findings reported for exposure to agricultural chemicals (pesticides), exposures which have been reported to be associated with ALS in at least some previous studies.[11 12] It is possible that the pesticide findings will be reported in future, in which case they should clearly refer to the previously published analyses for other occupational exposures and if necessary (mutually) adjust for these, and provide an overview of all occupational exposure analyses so that the picture will be complete.[13]

A limitation of the exposure assessment used in the Peters *et al* paper is that the NOCCA-JEM only uses (300) three-digit occupational codes, and occupational information (current job) was only recorded every 10 years. This hardly constitutes a rigorous and validation assessment of historical exposures. Using more detailed coding schemes such as International Standard Classification of Occupations 1968 (ISCO-68) (1506 five-digit codes), or International Standard Classification of Occupations 1988 (ISCO-88) (390 four-digit codes) would allow for a more detailed, valid and precise exposure classification. Nevertheless, exposure to specific pesticides, metals or solvents will be difficult to assess with JEMs and may require more individual-based exposure assessment and assignment by experts.

More epidemiological studies based on larger numbers of cases and better quality exposure assessment and assignment are likely to be more informative and provide better evidence on occupational and environmental risk factors for ALS. One approach to this would involve a two-stage approach with JEMs in combination with automatically assigned job-specific interview modules.[14] Furthermore, for chemicals with a long half-life in the human body (eg, polychlorinated biphenyl (PCB), metals) validation of exposure assignment is feasible as was recently shown.[11] More epidemiological studies based on large numbers of cases, but without the possibility of detailed exposure assessment will not be particularly informative and will certainly not provide the final verdict on occupational and environmental risk factors for ALS.

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REFERENCES

1 Pearce N, Kromhout H. Neurodegenerative disease: the next occupational disease epidemic? *Occup Environ Med* 2014;71:594–5.
2 Sutedja NA, Fischer K, Veldink JH, *et al*. What we truly know about occupation as a risk factor for ALS: a critical and systematic review. *Amyotroph Lateral Scler* 2009;10:295–301.
3 Huss A, Spoerri A, Egger M, *et al*. Occupational exposure to magnetic fields and electric shocks and risk of ALS: the Swiss National Cohort. *Amyotroph Lateral Scler Frontotemporal Degener* 2015;16:80–5.
4 Shaw I. Motor neurone disease—a methyl bromide exposure cluster points to a causal mechanism. *Hum Exp Toxicol* 2010;29:241–2.
5 Al-Chalabi A, Pearce N. Mapping the human exposome: without it, how can we find environmental risk factors for ALS? *Epidemiology* 2015;26:821–3.
6 Pearce N, Gallo V, McElvenny D. Sports-related head trauma and neurodegenerative disease. *Lancet Neurol* 2014;13:969–70.
7 Pearce N, Gallo V, McElvenny D. Head trauma in sport and neurodegenerative disease: an issue whose time has come? *Neurobiol Aging* 2015;36:1383–9.
8 Peters TL, Kamel F, Lundholm C, *et al*. Occupational exposures and the risk of amyotrophic lateral sclerosis. *Occup Environ Med* 2017;74:87–92.
9 Fischer H, Kheifets L, Huss A, *et al*. Occupational exposure to electric shocks and magnetic fields and amyotrophic lateral sclerosis in Sweden. *Epidemiology* 2015;26:824–30.
10 Park RM, Schulte PA, Bowman JD, *et al*. Potential occupational risks for neurodegenerative diseases. *Am J Ind Med* 2005;48:63–77.
11 Su FC, Goutman SA, Chernyak S, *et al*. Association of environmental toxins with amyotrophic lateral sclerosis. *JAMA Neurol* 2016;73:803–11.
12 Yu Y, Su FC, Callaghan BC, *et al*. Environmental risk factors and amyotrophic lateral sclerosis (ALS): a case-control study of ALS in Michigan. *PLoS ONE* 2014;9:e101186.
13 Kromhout H, Vermeulen R. Non-Hodgkin lymphoma and occupational exposures: multiple exposures not equal multiple papers. *Occup Environ Med* 2007;64:4–5.
14 Friesen MC, Lan Q, Ge C, *et al*. Evaluation of automatically assigned job-specific interview modules. *Ann Occup Hyg* 2016;60:885–99.

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