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Pesticides, Other Toxins Again Linked to Increased ALS

Pauline Anderson / May 11, 2016

Researchers have provided more evidence that exposure to toxic environmental pollutants raises the risk for amyotrophic lateral sclerosis (ALS). Unlike previous research, the new study used both surveys and measurement of toxic chemicals in blood. "This is not going to alter treatment at this point, but it really helps us think about the types of things we can do to prevent ongoing leakage of chemicals, and limit the pollution that we put into the environment, because it does have an impact, we believe, on disease," study author Stephen A. Goutman, MD, assistant professor and director, ALS Clinic, University of Michigan, Ann Arbor, told *Medscape Medical News*.

Dr Stephen A. Goutman

The study was published online May 6 in *JAMA Neurology*.

From a tertiary center in Michigan, researchers identified 156 patients with ALS and recruited 128 controls with no ALS or family history of any neurodegenerative disorder.

They determined likely exposures through self-administered questionnaires on occupational and residential history, and military service, and collected other information on smoking history and demographic characteristics.

From blood samples, they examined concentrations of 122 environmental organic pollutants, including organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs), which were chemicals used as coolants or lubricants in electrical equipment, and brominated flame retardants (BFRs).

Investigators accounted for confounding variables, including tobacco use, age, sex, education level, marital status, ethnicity, and military service.

The analyses showed a consistent association between occupational pesticide exposure and ALS. For any past exposure, the odds ratio (OR) was 5.09 (95% confidence interval [CI], 1.85 - 13.99; *P* < .01).

Ever having worked for the US Armed Forces was also associated with increased ALS risk (OR, 2.31; 95% CI, 1.02 - 5.25; *P* < .05).

Military Link

The link between being in the armed forces and ALS isn't new, said Dr Goutman. Theories possibly explaining the association include increased exposure to chemicals used during conflicts (especially during the first Gulf war), increased physical activity, multiple vaccinations, and traumatic injury.

Unexpectedly, occupational exposure to lead showed a statistically significant protective effect for ALS (OR, 0.32; 95% CI, 0.13 - 0.81; *P* < .05).

Dr Goutman said this requires additional follow-up but pointed out that lead was not measured in blood and that the protective effect was seen only when the authors looked at occupational exposure recalled over a lifetime, not at individual exposure time windows of susceptibility. "I don't think we can say at this point that lead is protective and people should go and expose themselves."

People are exposed to chemicals from levels in the air, water, soil, and food. Although most of the 122 chemicals that were studied have been banned, they are highly persistent in the environment. "Their half-lives are decades in the environment, and in humans, the half-lives are years to decades as well," said Dr Goutman.

And if someone was exposed to one of these chemicals, they were probably exposed to many others, said Dr Goutman. "These exposures all have correlations."

To get a better sense of "which chemicals are noise, or background pollution, and which are rising to potentially be involved in disease," the researchers did a multivariable regression analysis, said Dr Goutman.

A few chemicals stood out in the model: two OCPs (pentachlorobenzene and *cis*-chlordane), two PCBs (175 and 202), and 1 BFR (PBDE 47). These chemicals had *P* values of <.05 or <.01 in the imputed analysis.

But Dr Goutman cautioned about the role of individual chemicals in the development of ALS. "If you're exposed to, say, PBDE47, in isolation it may not necessarily cause any disease; however, if you mix that with other PBDEs or PCBs, those could have some augmentative effective that then becomes more toxic."

These results, said Dr Goutman, "need validation and repetition and confirmation."

Although the mechanisms are not fully understood, and the study does not prove causality, possible mechanisms linking environmental toxin exposure to ALS could include glutamate toxicity, apoptosis, and neuronal cell death.

"These are some of the concerns, but it doesn't explain at this point why there are different levels of susceptibility; in other words, why motor neurons are more susceptible than other cells," said Dr Goutman.

"It's too soon for us to pin down exactly what the direct mechanisms are that lead to the disease."

Case-Control Difficulties

In an accompanying editorial, Jacqueline J. Cragg, PhD, Department of Environmental Health, Harvard T.H. Chan School of Public Health, Merit E. Cudkowicz, MD, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, and Marc G. Weisskopf, PhD, Department of Epidemiology, Harvard T.H. Chan School of Public Health, all in Boston, say the study is important but illustrates some of the difficulties of carrying out case-control studies in ALS.

One of the difficulties, they write, is that questionnaire data are necessarily collected retrospectively. This raises concerns that cases and controls may recall past exposures differently and so introduce bias.

But the study's use of occupational history to assign past exposures is an important advantage of the study because occupational history is far less likely to be misreported by cases or controls, according to the editorial. Such an approach also makes it easier to examine exposures during specific periods, as the authors did. "This is an important strength of the study as it is a potentially important aspect of many exposures that is often ignored."

Another drawback with case-control studies is selecting an appropriate control population. The study used a volunteer database of people interested in research, but the "problem" is that people in such databases are often not typical of the general population, the editorialists write. "As the authors note, the controls in this study tended to be more educated and lived closer to the university where the research was conducted."

An important strength of the study, they write, is the comprehensive assessment of 122 different toxins in blood. This allows an "unprecedented ability to consider exposure mixtures and to attempt to identify compounds that are truly related to ALS rather than simply correlated with something else that is."

However, a difficulty with measuring compounds in biosamples collected in case-control studies is that the exposure of interest must have occurred before onset of the illness. A one-time measurement in blood of pollutants, even those with long half-lives, may not represent lifetime cumulative exposures.

When compounds are measured in biosamples collected after the disease has already occurred, the measured concentrations could be affected by the disease. "Thus, there is the potential for reverse causality," said the editorial.

For example, the kinds of organic pollutants measured in the study accumulate in fat. Studies have shown that persistent organic pollutant concentrations in serum, as well as in other tissues, increase after weight loss as they're released from fat stores and the reservoir for storing the compounds is decreased. "Because patients with ALS typically exhibit weight loss, this can greatly complicate the interpretation of findings when samples are being collected after disease onset."

However, if this was occurring in the study, it would be expected that all the fat-soluble compounds would be elevated in patients with ALS, which was not the case, they conclude.

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Abstract:

Association of Environmental Toxins With Amyotrophic Lateral Sclerosis

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Importance
Persistent environmental pollutants may represent a modifiable risk factor involved in the gene-time-environment hypothesis in amyotrophic lateral sclerosis (ALS).

Objective
To evaluate the association of occupational exposures and environmental toxins on the odds of developing ALS in Michigan.

Design, Setting, and Participants
Case-control study conducted between 2011 and 2014 at a tertiary referral center for ALS. Cases were patients diagnosed as having definitive, probable, probable with laboratory support, or possible ALS by revised El Escorial criteria; controls were excluded if they were diagnosed as having ALS or another neurodegenerative condition or if they had a family history of ALS in a first- or second-degree blood relative. Participants completed a survey assessing occupational and residential exposures. Blood concentrations of 122 persistent environmental pollutants, including organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs), and brominated flame retardants (BFRs), were measured using gas chromatography–mass spectrometry. Multivariable models with self-reported occupational exposures in various exposure time windows and environmental toxin blood concentrations were separately fit by logistic regression models. Concordance between the survey data and pollutant measurements was assessed using the nonparametric Kendall τ correlation coefficient.

Main Outcomes and Measures
Occupational and residential exposures to environmental toxins, and blood concentrations of 122 persistent environmental pollutants, including OCPs, PCBs, and BFRs.

Results
Participants included 156 cases (mean [SD] age, 60.5 [11.1] years; 61.5% male) and 128 controls (mean [SD] age, 60.4 [9.4] years; 57.8% male); among them, 101 cases and 110 controls had complete demographic and pollutant data. Survey data revealed that reported pesticide exposure in the cumulative exposure windows was significantly associated with ALS (odds ratio [OR] = 5.09; 95% CI, 1.85-13.99; *P* = .002). Military service was also associated with ALS in 2 time windows (exposure ever happened in entire occupational history: OR = 2.31; 95% CI, 1.02-5.25; *P* = .046; exposure ever happened 10-30 years ago: OR = 2.18; 95% CI, 1.01-4.73; *P* = .049). A multivariable model of measured persistent environmental pollutants in the blood, representing cumulative occupational and residential exposure, showed increased odds of ALS for 2 OCPs (pentachlorobenzene: OR = 2.21; 95% CI, 1.06-4.60; *P* = .04; and *cis*-chlordane: OR = 5.74; 95% CI, 1.80-18.20; *P* = .005), 2 PCBs (PCB 175: OR = 1.81; 95% CI, 1.20-2.72; *P* = .005; and PCB 202: OR = 2.11; 95% CI, 1.36-3.27; *P* = .001), and 1 BFR (polybrominated diphenyl ether 47: OR = 2.69; 95% CI, 1.49-4.85; *P* = .001). There was modest concordance between survey data and the measurements of persistent environmental pollutants in blood; significant Kendall τ correlation coefficients ranged from −0.18 (Dacthal and “use pesticides to treat home or yard”) to 0.24 (*trans*-nonachlor and “store lawn care products in garage”).

Conclusions and Relevance

In this study, persistent environmental pollutants measured in blood were significantly associated with ALS and may represent modifiable ALS disease risk factors.