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Voicing the need for ALS environmental research

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In 1962, Rachel Carson published *Silent Spring*, a book detailing the negative impact of widespread persistent pesticide use on the environment. The book led to public awareness of the damaging effects of pesticides, and it ignited the movement that would ultimately lead to the creation of the Environmental Protection Agency (EPA) in 1970. The book's title is a reference to pesticide-induced thinning of bird egg shells, leading to breakage, a reduction in bird populations, and the resulting loss of birdsong.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that leads to progressive weakness and acute disability that can physically silence persons living with the disease. Fortunately, those that treat, research, and advocate for persons with ALS will not be silenced, and it is with this impetus that we focus our attention on the environmental factors that influence ALS. This is of critical importance because we need to better elucidate ALS pathomechanisms to identify modifiable disease risks to lower incidence and develop treatments to improve patient outcomes.

Ongoing genetic discoveries have been, and continue to be, extremely important for advancing our understanding of ALS pathogenesis. Furthermore, evolving technologies along with global collaborations have accelerated genetic discoveries. Despite these achievements, it is possible we are only telling half of the story. In the roughly 90% of individuals without a family history (sporadic cases), ALS heritability--how much genetic variability contributes to disease--is estimated to be between 20–60%. Additionally, even for individuals with a known genetic mutation, additional "steps" are required to cause disease, since some carriers do not develop ALS.[1] Specifically, environmental triggers, superimposed on genetic risk and cellular changes due to aging,[2] are widely believed to play a role in ALS. The basic premise is that the more prevalent genetic variants are less penetrant, but that they may be activated through a certain environmental exposure. Thus, high-prevalent/low-penetrant genetic traits can become highly penetrant following exposure to specific toxicants. Aging may further interact with these effects as the cumulative exposure to various sources of pollution will increase.[3]

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Drs. Stephen Goutman and Eva Feldman from University of Michigan contend that increased attention to ALS environmental research is necessary to identify modifiable disease risks and drug targets for ALS.

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Dr. Goutman has provided medical advisory for Biogen and ITF Pharma. Dr. Feldman sits on an advisory board for Novartis.

Among the possible environmental ALS risks, our group has recently reported that pesticides increase ALS risk[4, 5] and that higher concentrations of persistent organic pollutants are associated with a poorer ALS survival.[6] However, more work must be done to fully identify and catalog what environmental factors influence disease risk and progression. In other words, we must define the ALS exposome, the cumulative measure of life-long exposures and how they relate to ALS onset and progression. This is not a simple task because it essentially requires us to quantify all environmental exposures from the earliest stages prior to disease onset and throughout ALS development. When *Silent Spring* was released, President John F. Kennedy commissioned a scientific advisory panel to help understand the environmental effects of pesticides.[7] Despite the difficulties that accompany performing these environmental studies, the ALS community has chosen to persevere and accept the challenge to conduct exposome research, just as Kennedy challenged us to aim for the moon.

There are real barriers to performing this work. It requires establishing extremely large prospective cohorts at birth to monitor the development of a disease as rare and heterogeneous as ALS, which is cost prohibitive. For case-control studies, it is costly and challenging to identify willing and motivated controls, especially for a disease without significant public awareness. Further, there are multiple debates over what comprises the best control population, and these debates can delay funding and slow research progress. But, just as the cost and efficiency of genetic research in ALS has improved over time, our hope is that it will be the same for exposome research.

What are the steps that we can take presently? All ALS stakeholders should encourage participation in the National ALS Registry (https://www.cdc.gov/als) in order to improve case ascertainment, better track disease, and build the knowledgebase and cohorts necessary for this research. Informing our patients of the importance of National ALS Registry enrollment is a standard practice in our clinic, and this practice should be incorporated into other clinics. We are impressed by efforts of the National ALS Registry, as well as the ALS Association and Muscular Dystrophy association, to support the Registry and encourage other healthcare professionals to support these efforts.

We propose the following actions to address the above barriers moving forward. With the exception of Massachusetts (https://www.mass.gov/als-registry), ALS is not a reportable disease in the United States; therefore, we do not know the true annual incidence or whether it is increasing, as many ALS researchers suspect. We advocate to follow Massachusetts' lead and make ALS reportable in all states. This approach will lead to better case ascertainment and subsequent scientific advancements. Mandatory reporting should be accompanied by funding support to ensure programmatic success. It should also be extended to enable occupational and exposure assessments for individuals with ALS, and to perform geospatial analyses to assess for clustering of ALS cases and whether cases cluster around superfund sites and bodies of water. Improved funding for ALS exposome research is thus required. The need likewise remains for the funding of smaller hypothesis generating studies, as findings from these smaller studies can then leverage data from larger ALS cohorts. Advocacy at the state and national level by citizens can help voice the need for these changes.

If these recommendations are enacted, we will have improved knowledge of whether more people are developing ALS, what public policy efforts are needed to address ALS risks, and how much research dollars should be allocated. In addition, if we are able to identify environmental triggers, efforts can be made to minimize these exposures and prevent new ALS cases. Additionally, given the concerns for environmental triggers for both Parkinson's and Alzheimer's disease, the public health impact may extend beyond ALS to other neurodegenerative diseases, and even more broadly.

While the incidence of ALS is relatively uniform in European based populations, the worldwide number of ALS cases is anticipated to rise by 69% by 2040, represented by a 34% increase in the United States secondary to an aging population.[8] However, as previously noted, aging is also associated with greater cumulative environmental exposures.[3] Further, pollutants are a global concern, as they reach areas of the world where they have previously never been used.[9] Therefore, we should be open to the possibility that a reduction of environmental risks could potentially reduce the global burden of ALS, an idea that parallels efforts to reduce dementia by reducing air pollutation.[10]

As the EPA celebrates its 50th birthday in 2020, the World Health Organization declares that air pollution and climate change are among the top ten threats to global health. Clearly, all the facts point to a need for improved awareness of the integral links between the environment and neurological diseases. How does exposome research improve our understanding of ALS and more broadly human health? Insights into ALS mechanisms that are influenced by environmental triggers will pave the way for a better understanding of gene-environment interactions and ALS disease triggers. Equipped with this knowledge, we can learn how to minimize exposure to lower incidence and identify druggable targets to treat patients. Further, the ability to identify specific environmental toxins can promote cleanup efforts and public awareness campaigns. The time to act is now.

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