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Hypothesis: amyotrophic lateral sclerosis and environmental pollutants

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Abstract

Genetic, epigenetic, and environmental factors are relevant in the causation of amyotrophic lateral sclerosis (ALS) in a multistep cascade. We suggest that exposure to environmental pollutants in early life is one such factor. ALS was first described in the 19th century in the context of the Industrial Revolution that began more than 50 years earlier. The rising incidence of ALS thereafter correlates with increasing longevity, but this is an incomplete association. We suggest that increasing exposure to environmental pollutants due to industrial activity, acting over a lifetime, is also important. The combination of genetic mutations and pollutant exposure, with increased life expectancy, may account for the apparent variations in incidence of the disease in different countries and continents and even regionally within a given country. This hypothesis is testable by focused epidemiological studies, evaluating early and lifelong industrial pollutant exposure of differing types, within the Bradford Hill framework.

KEYWORDS

ALS genetics, ALS pathogenesis, amyotrophic lateral sclerosis, environmental pollution, multistep process

1 | INTRODUCTION

> A discovery is usually an unforeseen relation not included in theory, for otherwise it would have been foreseen—Claude Bernard (1865)[1]

Amyotrophic lateral sclerosis (ALS) was first recognized in the mid-19th century,[2] when an environmental causation was considered likely.[3] Recent research has implicated genetic factors.[4] Downstream errors in messenger RNA, the slow build-up of proteinaceous debris in neuronal cytoplasm and the proteasome, slowed axonal transport, and undetermined environmental factors are all credible determinants of the ALS syndrome.[4] The various issues in attributing environmental or workplace associations to any disease causation have been addressed by Bradford Hill (Table 1).[5] Although ALS usually presents in middle or later life, preclinical genetic, epigenetic, and environmental influences are significant.[6] The overt syndrome progresses relatively rapidly, causing death in most patients within 5 years of diagnosis.[7]

There are only four accepted associations: age; male sex; tobacco smoking; and a history of physical exercise.[8] Unexplained hypermetabolism may cause weight loss in the preclinical stages of the disease.[8] Suggested dietary associations may represent confounders linked more closely with diet in general than with ALS itself.[9] Any environmental risk factor must be relevant in the context of altered brain metabolism consequent on genetic factors, such as *SOD1* mutations, *C9orf72* DNA repeats, or epigenetic changes. The many genetic mutations known to be associated with ALS imply differing cellular/neuronal metabolic abnormalities.[4] Indeed, the ALS syndromes associated with these mutations differ somewhat from each other.[7] The clinically sporadic form of ALS is sometimes unexpectedly associated with a recognized mutation.

Abbreviations: ALS, amyotrophic lateral sclerosis; BMAA, β-*N*-methylamino-L-alanine; CNS, central nervous system; PM, particulate matter; PYFU, person-years of follow-up.

TABLE 1 Bradford Hill's nine criteria for testing a putative causative association of a potential environmental factor with a disease[5]

The nine criteria	Methodological cautions	Weights for ALS
Strength of association	Remember possibility of secondary associations	Good, but more evidence required
Consistency of association	Replication should be sought in differently designed studies, both retrospective and prospective	Suggestive
Specificity of association	Remember there may be multiple causations of a disease	Weak
Temporality of association	Disease must follow exposure	Suggestive
Biological gradient of association	Dose-response relationship is important, but large doses may cause different syndromes compared with small doses	Testable
Plausibility of association	Not necessary, but helpful	Reasonable
Coherence of association	Cause-and-effect relationship should not conflict with other general facts	Adequate
Experimental test of association	A testable hypothesis can generate firm evidence	Consistent and testable
Analogy with other toxicities	Compare putative association with other recognized associations	Testable

Note: Weightings for ALS in the third column represent our assessments for environmental pollutants.
Abbreviation: ALS, amyotrophic lateral sclerosis.

2 | CONTEXT OF EARLY DESCRIPTIONS OF ALS

Progressive muscular wasting, as a clinical syndrome, was recognized by Sir Charles Bell (1774-1842) and his contemporaries,[10] amid controversy regarding its primary muscular or myelopathic causation. The first recognizable description of ALS was given by Cruveilhier in 1853.[11] Atrophy of the anterior spinal nerve roots was stressed by Charcot,[3] and the syndrome began to be recognized in Paris from about 1865.[2] There are early descriptions, with pathology, from England.[12] ALS became defined clinically by muscular wasting with fasciculation and stiffness, and by the loss of anterior horn motor neurons and corticospinal tract degeneration, with involvement of central nervous system (CNS) frontal and callosal pathways, found at autopsy.[11,12] The formal neurological examination, with testing of the ankle and knee jerks, did not enter clinical practice until the 1890s, and therefore modern diagnostic criteria for ALS cannot be applied before that time. For example, there are no ALS-like descriptions in Thomas Willis's 17th century detailed case books or lectures.[13]

3 | AGE STRUCTURE OF 19TH CENTURY POPULATIONS

The rarity of ALS before the mid-19th century is conventionally attributed to the population demographic at that time (Figure 1), determined by high mortality rates in infancy and midlife.[14] In 1845, 45% of the population of England and Wales were less than 20 years old and only 7% were older than 60, but during the 19th century there were profound socioeconomic changes. In the 18th century, more than half the population was employed on the land, but by 1840 only about 25% were engaged in agricultural labor. The UK population increased from about 6.5 million at the end of the 17th century to more than 9 million in 1800, of whom about 600 000 lived and worked in London and only 50 000 to 75 000 in the newly developing industrial towns. However, the 1901 census population of Great Britain and Ireland was estimated at 41 million, of whom 6.5 million lived and worked in London and many more in the smoky industrial Midlands.[14]

In 1841 survival beyond the first 5 years of life conferred an approximately 40% chance of survival to age 50,[14] but, as in all life statistics, the longer someone survives the greater the chance of continued survival (Figure 1). However, survival to the peak age for ALS diagnosis, the sixth and seventh decades,[15] was less frequent in Victorian Britain and other European countries than the current British expectation of over 90%.[14] In less developed countries life expectancy continues to be shorter.[14] These demographics suggest that ALS would have been less commonly encountered in the mid-19th century, although precise figures are speculative. Nonetheless, some cases of younger age were recognized from the time of Charcot's description (see Table 1 in the study by Turner et al[16]).

4 | ENVIRONMENTAL POLLUTANTS AND ALS RISK

Industrialization has been accompanied worldwide by a build-up of a complex mix of environmental pollutants in land, sea, and air.[17] In older economies, such as Britain and many other developed Western countries, recent decreasing coal- and wood-based industrial and domestic usage contrasts with new coal-based economies in countries such as China and India. This evolving pattern of energy usage has been described as the environmental Kuznets curve,[18] representing transformation from a clean agrarian economy to a polluting industrial economy, and then further evolution to a clean service economy. The curve predicts that pollution-related disorders will become more common in newly industrializing societies and less common in older industrialized economies, after a long lag period, while the environment becomes cleaner.

Defining relevant environmental pollutants, especially those acting many years before an inquiry, is not easy. For example, cigarette smoke, a recognized risk factor for ALS,[19] contains more than 3,500

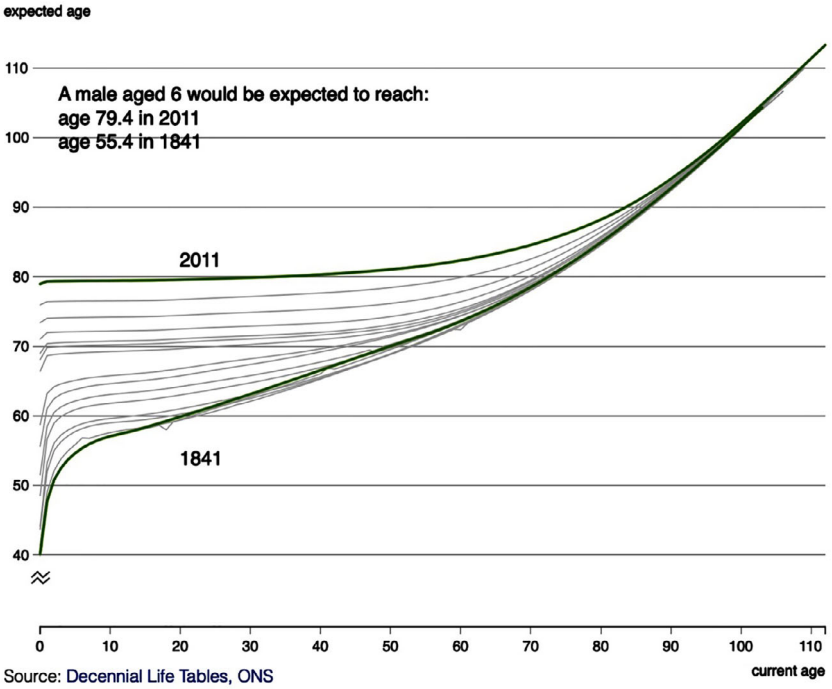

FIGURE 1 Curves show both the effect of infant mortality and relatively short adult life expectancy in the population of England and Wales in 1841 compared with 2011. Relatively few people survived to their sixth decade or beyond in the 1841 cohort. The series of curves represent data for each decade between 1841 and 2011 (Office for National Statistics, United States, "How has life expectancy changed?" 2015) [Color figure can be viewed at wileyonlinelibrary.com]

different constituents, including pesticides, free radicals, nitric oxide, and many hydrocarbon compounds, so it is difficult to know which are of major importance.[20] Industrial pollution consists of a mix of organic and inorganic chemicals, insecticides, and different types of particulates, dusts, and discarded multiconstituent debris, including metals and plastics, contaminating air, water, and soil. For most of these potentially harmful substances, very few data exist regarding their toxicity to the human nervous system. However, persistent organic pollutants, especially polybrominated diphenyl esters and polychlorinated biphenyls, have been associated with reduced survival in patients with ALS, independent of age of onset and other covariates.[21] Thus far, epidemiological studies of potential environmental risk factors for ALS have tended to be small and focused on current occupational exposures, rather than on lifelong and early life exposures.[22] Occupational exposures to lead, pesticides, and solvents have been weakly associated with ALS in some studies, but these associations were excluded in carefully controlled studies.[23] In retrospective studies dietary factors have been weakly associated with ALS.[24]

Because ALS begins insidiously, probably in early life,[6] pollutant exposures in childhood and adolescence are likely to be important, given a susceptible genetic background.[4] Barker identified the period from conception through childhood as critical for human development, determining lifelong patterns of health and disease, not only for ischemic heart disease and type 2 diabetes (metabolic syndrome X), but also for neurological disorders, such as schizophrenia and autism.[25] Fine particulate air pollution ($PM_{2.5}$ and $PM_{<10}$), both man-made and from natural sources, is a major environmental hazard, especially in young persons.[17] Particle size and exposure duration are key determinants of adverse health effects. Particles less than 2.5 μm ($PM_{2.5}$) pose the greatest threat to health as they may pass through the lungs into the bloodstream and thus access the brain. Exposure to $PM_{2.5}$ has been linked to oxidative stress and increased levels of systemic and multiorgan inflammation[26] and may contribute to early decline in memory, with concomitant early loss of cerebral gray matter.[27] Many everyday human activities, such as energy generation, transport, industrial processes, farming, and domestic heating, are polluting. Forest and crop burning and transport are particularly hazardous for air quality. Coal burning entered into large-scale use during the Industrial Revolution, both for domestic heating and for industrial steam power and electricity generation. The resulting smog and soot had serious short- and long-term health effects, such as the 1952 London smog,[28] but delayed effects of early-life exposure are less well studied.[20,29] Exposure to organic pollutants during the sensitive neurodevelopmental period has been suggested as a cause of epigenetic neurodevelopmental disorders and perhaps also of late-onset neurodegeneration in later life.[29,30] It is relevant to note that a reduced sociodemographic index (a composite of income, educational attainment, and fertility rate) has been associated with more disability-adjusted life-years lost due to motor neuron diseases, suggesting an increased incidence with low income and poor living conditions.[31]

5 | ALS EPIDEMIOLOGY

The incidence of ALS has been studied in many different populations. On the island of Guam, an ALS/parkinsonism disorder associated with ingestion of toxins derived from edible cycad seeds, namely β-*N*-methylamino-L-alanine (BMAA) and related compounds, has become rare as dietary habits among Guamanian Chamorros change,[32] but BMAA, probably absorbed from groundwater contaminated with

cyanobacteria, has also been found accumulated in brains of North Americans with ALS and Alzheimer disease.[33] Kondo[34] found an increased incidence of ALS in Japan between 1940 and the 1960s, with a declining incidence to baseline after this period. He suggested this may be related to major adverse socioeconomic events in Japan during the Second World War. Epidemiological studies in European, Middle Eastern, Asian, Caribbean, and Latin American countries[35-41] have reported a recent increased incidence of ALS, not explicable by population aging.[36,42] Despite inevitable inconsistencies in study methodology and case ascertainment, ALS has emerged as more common in Northern European populations (1.89: CI 1.46-2.32 per 100 000 person-years follow-up [PYFU]), with lower incidence rates in East Asia, China, and Japan (0.83: CI 0.58-0.89 per 100 000 PYFU), and in South Asia and Iran (0.73: CI 0.42-0.89 per 100 000 PYFU). Incidence rates in Europe, North America, and New Zealand were found to be concordant with each other.[42-44] Hispanic heredity, for example, in Cuba, Spain, and South America, is associated with a lower risk.[41,44] Marin et al[44] concluded that comprehensive international studies were needed, using standardized case ascertainment, to investigate possible links between ancestry, environment, ALS incidence, and phenotype. We recommend that such studies should include analysis of pollutant exposure in air, water, and food, emphasizing lifetime data.[6,16,25] Other exogenous risk factors in the pathogenesis of ALS have been excluded as common causations.[22,33] Curiously, alcohol ingestion may even be protective,[45] whereas tobacco smoking shows a dose-response relationship to ALS.[22] An increased incidence of early-onset ALS has been reported in Italian soccer players, but the effect size is small.[46] However, ALS presents more frequently with focal involvement of the dominant arm, a feature that may follow greater usage.[47]

6 | GENETIC AND ENVIRONMENTAL INTERRELATIONSHIPS

Al-Chalabi and Hardiman[4] suggested a disease model "in which ALS is considered the result of environmental risks and time acting on a pre-existing genetic load, followed by an automatic, self-perpetuating decline to death." This concept defines ALS as a syndrome in which a "tipping point" of metabolic abnormality is reached, leading to clinical presentation. This could be associated, for example, with gradual accumulation of prionlike, propagating protein aggregates in neuronal cells, spreading by seeding from cell to cell.[48] The three recognized major classes of "prionoid aggregation" in ALS (TDP43, FUS, and SOD1) are mutually exclusive pathologies but they are associated with similar, yet variable, ALS phenotypes.[49,50] Age is the most prominent association.[4,51] The early-life environmental factors leading to the development of ALS are undefined, but the slope of a regression analysis of log incidence against log age at diagnosis has suggested a six-step process leading to overt sporadic ALS.[52,53] Fewer steps were calculated as being required in ALS associated with *C9orf72* (three steps), *TARDBP* (four steps), and *SOD1* (two steps) mutations,[54] suggesting different metabolic cascades. The traditional distinction between genetic and sporadic ALS is therefore blurred.[55]

7 | TESTING THE HYPOTHESIS

We weighted the Bradford Hill criteria for environmental factor(s) in the causation of ALS in relation to our hypothesis in Table 1. If early or lifelong environmental pollution is a risk factor for ALS, its incidence will proportionally increase in developing countries because of pollutant exposure associated with forest burning, oil and coal burning, and other manufacturing and transport-related activities. In developed countries, where air pollution is likely to improve, the incidence of ALS may slowly decline after a delay of several decades, although this may be modified by global distribution of airborne pollutants. The incidence of ALS should therefore approximate the kinetics of the environmental Kuznets curve. Although formal case-control studies of ALS in developing societies are lacking, our hypothesis can be tested using incidence data from developed Western countries among communities of adult immigrants from low-incidence areas compared with their offspring, born and brought up in the West, while checking relevant environmental and genetic information.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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