

Risk factors for amyotrophic lateral sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease. It is typically fatal within 2–5 years of symptom onset. The incidence of ALS is largely uniform across most parts of the world, but an increasing ALS incidence during the last decades has been suggested. Although recent genetic studies have substantially improved our understanding of the causes of ALS, especially familial ALS, an important role of non-genetic factors in ALS is recognized and needs further study. In this review, we briefly discuss several major genetic contributors to ALS identified to date, followed by a more focused discussion on the most commonly examined non-genetic risk factors for ALS. We first review factors related to lifestyle choices, including smoking, intake of antioxidants, physical fitness, body mass index, and physical exercise, followed by factors related to occupational and environmental exposures, including electromagnetic fields, metals, pesticides, β -methylamino-L-alanine, and viral infection. Potential links between ALS and other medical conditions, including head trauma, metabolic diseases, cancer, and inflammatory diseases, are also discussed. Finally, we outline several future directions aiming to more efficiently examine the role of non-genetic risk factors in ALS.

Keywords: amyotrophic lateral sclerosis, risk factors, genetics, lifestyle, environment

Introduction

Amyotrophic lateral sclerosis (ALS) is an adult-onset, fatal neurodegenerative disorder, characterized by degeneration of both upper motor neurons in the primary motor cortex and lower motor neurons in the brainstem and spinal cord. Symptoms of ALS initially include muscle atrophy and weakness. Subsequently, spreading paralysis of the voluntary muscles, and eventually the respiratory muscles, often develops.¹ Approximately 50% of patients with ALS die within 30 months of symptom onset, often from respiratory insufficiency,^{2,3} whereas about 10% of patients may survive for more than a decade.⁴

ALS has recently been recognized as a multi-system disorder rather than a disease limited to motor neurons. Some ALS patients may show extrapyramidal features such as tremor, rigidity, propulsion, and impaired postural reflexes.^{5,6} In about one quarter of ALS patients, the disease is associated with subtle cognitive deficits. In addition, 3%–5% of ALS patients are diagnosed with frontotemporal dementia (FTD),⁵ a dementia of non-Alzheimer's type with symptoms of behavioral changes, frontal executive deficit, and impaired handling of language.⁷ ALS and FTD are related conditions and overlap clinically, pathologically and genetically.^{8,9} The link between ALS and dementia may not be restricted to FTD though, as several epidemiological studies have shown a higher risk of dementia among families of ALS patients in general^{10–13}

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and among families of ALS patients carrying an expanded hexanucleotide repeat in *C9ORF72* specifically.¹² Given the modest increment in risk observed for dementia among ALS families, and the lack of genotyping data for ALS in most previous studies, more research is needed before a firm conclusion regarding familial aggregation of ALS and dementia can be drawn.

About 10%–15% of ALS patients have a familial form of the disease, with at least two first-degree or second-degree relatives with ALS.¹⁴ If no family history is identified, the diagnosis is assumed to be sporadic. The incidence of sporadic ALS shows little variation in the Western countries, ranging from 1 to 2 per 100,000 person-years,^{15–18} with an estimated lifetime risk of 1 in 400.¹⁹ ALS is rare before the age of 40 years and increases exponentially with age thereafter. Mean age at onset is 58–63 years for sporadic ALS and 40–60 years for familial ALS,^{20–26} with a peak incidence in those aged 70–79 years.^{24–27} Men have a higher risk of ALS than women, leading to a male-to-female ratio of 1.2–1.5.²⁸ During recent decades, an increasing incidence of or mortality from ALS has been reported in Sweden,^{27,29,30} Finland,³¹ Norway,^{32,33} France,³⁴ the USA,^{35,36} and other countries,^{37–39} although an increase is less obvious in other studies.^{40–44} More research is needed to exclude alternative explanations for the suggested rise in incidence, including for example increasing awareness in the general public of ALS as a disease and better diagnosis of ALS in different neurologic settings.

Geographic foci of the Western Pacific form of ALS, mainly in Guam and the Kii Peninsula of Honshu Island, Japan, have been reported, with a prevalence 50–100 times higher than in other parts of the world.^{45,46} This form of ALS presents in three clinical forms, ie, ALS, atypical Parkinsonism with dementia, and dementia alone, known collectively as the ALS-Parkinson's dementia complex (ALS-PDC). The cause of these aggregations remains elusive, and a decreasing prevalence of ALS-PDC was noted recently.⁴⁵

There is no cure for ALS to date. Riluzole, a presumed glutamate antagonist, is the only drug approved by the US Food and Drug Administration for the treatment of ALS, but the exact mechanism of action of riluzole is as yet unclear. It appears to prolong ALS survival by a few months on average, although when given at an early stage or to younger patients, it might prove more effective.^{47,48}

Risk factors for ALS

A handful of factors have been proposed to be associated with ALS; however, the only established risk factors to date are older age, male sex, and a family history of ALS.⁴⁹ In this

review, we focus on several of the most frequently studied risk factors for ALS.

Familial aggregation

Family and twin studies are powerful tools for identifying a heritable component of different diseases. A disease is considered to aggregate in a family if the risk of developing the same disease is high among the relatives of an index patient compared with individuals unrelated to the index patient. Early case-control studies found that families of ALS patients had a 3-fold⁵⁰ to >10-fold⁵¹ risk of ALS. A Swedish twin study identified two of 26 monozygotic twin pairs with concordant ALS, but none in 51 dizygotic twin pairs, leading to a relative risk of 153 for monozygotic co-twins of ALS patients, compared with the general Swedish population.⁵² Pooling several twin registers from Sweden and the UK, the heritability for ALS is estimated at 61%.⁵³

Genetic risk factors

The inheritance patterns of ALS vary depending on the mutation, although there is often a Mendelian pattern and high penetrance in familial ALS. The two major genetic contributors to ALS known to date are the *C9ORF72* gene and the *SOD1* gene, but there are also a number of other genes associated with ALS, although not to the same extent (more information available at the Amyotrophic Lateral Sclerosis Online genetics database, <http://alsod.iop.kcl.ac.uk/>). Several excellent review articles have recently discussed ALS genetics in detail.^{54,55} In the present review, we focus on the *C9ORF72*, *SOD1*, and *TARDBP* genes, which are to date the most important genes identified in familial ALS cases.

Chromosome 9 open reading frame 72

The *C9ORF72* gene, the function of which is as yet unknown, is located on chromosome 9. A mutation in this gene has been shown to cosegregate with both ALS and FTD in studies of American, European, and Japanese patients.^{56–59} The mutation is an expansion of a hexanucleotide repeat sequence, GGGGCC, in a non-coding part of the gene. In ALS patients, the number of repeats can be more than a thousand, in contrast with 2–30 repeats in control populations.⁵⁶ Multiple studies have demonstrated that ALS and FTD phenotypes are associated with the *C9ORF72* GGGGCC hexanucleotide repeat expansion.⁵⁷ The prevalence of the mutation is variable across countries; it is related to up to 40% of familial ALS in the USA and Europe, and up to 7%–11% of sporadic ALS.^{8,56,60} Recently, 20% of ALS patients identified from the Kii Peninsula of Japan were found to carry this repeat expansion,

compared with less than 2.5% in the rest of Japan, indicating that it may partially account for the high incidence of ALS-PDC in this geographic focus.⁶¹ The repeat expansion mutation in the *C9ORF72* gene may result in a decreasing amount of functional C9ORF72 protein, and may therefore be a loss-of-function mutation.⁶² However, *C9ORF72* may also be a toxic gain-of-function mutation; for example, the RNA transcribed from the repeated region might accumulate in the nucleus and interfere with cell function.⁵⁶

CuZn-superoxide dismutase

Mutations in the *SOD1* gene are found in 10%–20% of familial ALS cases and 1%–5% of sporadic ALS cases globally.⁶³ CuZn-superoxide dismutase (SOD1) is one of three superoxide dismutase isoenzymes responsible for the conversion of free superoxide radicals to molecular oxygen and hydrogen peroxide. To date, more than 170 mutations of *SOD1* have been identified in ALS.^{55,64} Most *SOD1* mutations are inherited in a dominant manner, except for the D90A mutation, which is the most common *SOD1* mutation worldwide and is inherited in both a dominant and a recessive manner.^{65,66} Animal studies have shown that transgenic expression of human *SOD1* mutations in rodents results in a motor neuron disease phenotype, whereas knockout of the *SOD1* gene in these rodents does not,^{67–69} suggesting that the pathogenicity of *SOD1* mutations does not involve loss of function, but rather a gain of a toxic function. This toxicity may be due to the formation of aggregates caused by the instability of the protein.^{70,71}

TAR DNA binding protein

The *TARDBP* gene is located on chromosome 1 and codes for the DNA-binding and RNA-binding protein TDP-43. To date, 30 mutations of this gene have been found in about 5% of patients with familial ALS and 1% of patients with sporadic ALS.^{72–78} In healthy neurons, TDP-43 is located in the nucleus and functions as both a DNA-binding and an RNA-binding protein. TDP-43 is involved in transcription and RNA processing, including splicing and maintenance of mRNA stability, and transport of subcellular RNA.^{79–81} When mutated, TDP-43 is cleaved and abnormally phosphorylated, and accumulates in ubiquitinated cytoplasmic inclusions in motor neurons of patients with familial ALS, sporadic ALS, or FTD.^{9,82}

Lifestyle risk factors

Smoking

According to an evidence-based medicine analysis, smoking is the only probable risk factor for ALS.^{49,83}

Intriguingly, smoking may be a risk factor among women, especially post-menopausal women,^{84,85} although not among men.⁸⁶ The controversy regarding the role of smoking in ALS appears to remain unsolved^{87,88} and is an interesting area for epidemiological studies of ALS.⁸⁹

Dietary factors

The most investigated relationship between dietary factors and ALS is the inverse association between higher intake of antioxidants and a lower risk of ALS. For example, regular use of vitamin E supplements was associated with a lower risk of ALS,⁹⁰ and a longer duration of vitamin E use was associated with a lower risk of ALS in a large study pooling individual data from five cohorts.⁹¹ Dietary intake of vitamin E was also associated with a lower risk of ALS in case-control studies from the Netherlands⁹² and Japan.⁹³ These results were further corroborated by another cohort study that measured vitamin E serum levels directly.⁹⁴ In other smaller studies, however, levels of vitamin E did not differ between ALS patients and controls, neither in the cerebrospinal fluid (CSF)⁹⁵ nor in the serum^{95,96} samples. Further, high-dose vitamin E as an add-on therapy to riluzole in ALS did not extend survival, although improvement in the rate of deterioration of function was suggested for vitamin E.⁹⁷ Another group of antioxidants associated with a lower risk of ALS is polyunsaturated fatty acids,^{92,98,99} which may modulate lipid metabolism, oxidative stress, and inflammatory processes. Evidence for the role of other dietary factors in ALS, including consumption of coffee^{100,101} and alcohol,^{102,103} is scant.

Body mass index and physical fitness

There is a strong clinical impression that ALS patients have a higher level of physical fitness and lower body mass index (BMI) than average.¹⁰⁴ Whether there is an overrepresentation of higher physical fitness among presymptomatic ALS patients is not firmly established. However, based on a large sample of Swedish conscripts, one longitudinal study showed that higher physical fitness, but not muscle strength, measured at age 18 years was associated with a higher risk of ALS decades later.¹⁰⁵ Low BMI and higher BMI reduction rate have been shown to be independent prognostic indicators for ALS after diagnosis.^{106–108} Longitudinal cohort studies further suggest that low pre-morbid BMI is associated with a higher risk of and greater mortality from ALS.^{109,110}

Athleticism, chronic traumatic encephalopathy, and physical exercise

Historically, the most famous ALS patient was Lou Gehrig, the renowned US baseball player. Several studies have

demonstrated increased risk of ALS among football or soccer players,^{111–114} other athletes,¹¹⁵ and individuals who engage in vigorous physical activity,¹¹⁶ but inconsistent results have also been reported.^{117–120} Strenuous physical activity, repeated head injuries, use of illicit performance-enhancing drugs, or chemicals used to treat football fields have all been discussed as potential explanations for such risk elevations.^{111,121} Chronic traumatic encephalopathy, a newly defined neurodegenerative disease, often resulting from repeated head injuries, has been proposed as the underlying reason or the “correct” diagnosis for ALS cases observed among professional athletes and perhaps also among military veterans.¹²² Different levels of physical exercise (professional versus recreational) may have very different biological effects on neurodegeneration. This is in line with previous findings of an increased risk of ALS among professional football players,^{111–114} although not among high school players.¹¹⁹ Similarly, a large European case-control study showed a 51% lower risk of ALS for organized sport, but a 59% higher risk of ALS for professional sport.¹²³ Further efforts to disentangle the different exposure patterns involved in professional sports as compared with recreational sports will be needed to better understand these findings. Although the hypothesis that athleticism contributes to ALS is intriguing, caution should be exercised in interpreting these findings, given the fact that the vast majority are based on small numbers of ALS cases.

Occupational and environmental risk factors

Occupations

Workers in various occupations with seemingly disparate exposures have been reported to be potentially at altered risk of ALS, including athletes, carpenters, cockpit workers, construction workers, electrical workers, farm workers, hairdressers, house painters, laboratory technicians, leather workers, machine assemblers, medical service workers, military workers, nurses, power production plant workers, precision metal workers, programmers, rubber workers, shepherds, tobacco workers, veterinarians, and welders.^{124,125} These occupations potentially involve work exposures to chemicals, pesticides, metals, and electromagnetic fields (EMF).^{125–127} However, common denominators among these different occupations are not easily identified.

Military personnel are exposed to a battery of unique and potentially harmful factors, including physical and psychological exertion and trauma, transmissible agents (eg, viruses) and vaccines, toxic substances (eg, heavy metals and chemicals), and other environmental toxicants specific to

particular deployment areas. A review article focusing on the potential links between military-related factors and ALS has been published recently, and concluded that although there is evidence suggesting a role of military service in ALS, it is too premature to draw a firm conclusion regarding a causal relationship.¹²⁸

Electric occupation, electric shock, and electromagnetic field

ALS has been associated with “electrical” occupations,^{129,130} especially welding.¹³¹ Magnetic fields, electrical fields, contact currents, microshocks, and both perceptible and imperceptible electric shocks all contribute to occupational exposure to extremely low frequency EMF. The reported association of ALS with EMF is generally weaker than that with electrical occupations.^{129,130} Evidence is not yet available to distinguish whether electric shocks or exposure to EMF underlies the association between electrical occupation and ALS.^{132–134} A meta-analysis suggested that there might be a slight but statistically significant increase in ALS risk among people with job descriptions related to relatively high levels of EMF exposure.¹³⁵ However, studies using residential proximity to power lines as a proxy for EMF exposure have failed to support such a relationship.^{136,137} Different exposure levels investigated in studies of occupational, compared with residential, exposure to EMF may partly explain the different findings to date.

Metals

That lead may be a culprit in ALS etiology is a long-standing hypothesis. Previous studies have mostly supported this relationship, relying in general on indirect measures of lead exposure.^{115,138–148} Lead levels in both blood and bone were found to be associated with ALS,^{147,148} although others found only an association for blood and not bone.¹⁴⁹ Blood lead levels may reflect current environmental lead exposure and may also reflect mobilization of lead from bone.¹⁵⁰ Lead toxicokinetics and bone metabolism may therefore modify the lead-ALS association. A recent case-control study observed that blood lead levels were high among ALS cases compared with controls, even after careful adjustment for bone turnover status and a polymorphism affecting lead toxicokinetics.¹⁵¹

The neurotoxic properties of manganese are well known.¹⁵² Manganese crosses barrier systems at the choroid plexus and accumulates in the central nervous system, with a longer half-life in nervous tissue. Welders exposed to manganese demonstrate motor impairments in general¹⁵³ and impaired fine motor skills specifically.¹⁵⁴ Manganese concentrations in CSF samples of ALS patients were significantly elevated

(median 5.67 $\mu\text{g/L}$) compared with healthy controls (median 2.08 $\mu\text{g/L}$).¹⁵⁵ Furthermore, manganese concentrations were higher in the CSF than in the plasma of ALS patients, suggesting a transport of manganese into the central nervous system in ALS.¹⁵⁵

Iron serves as a cofactor for regulatory enzymes in the electron transport chain in the mitochondria. Brain iron content increases with age, and iron accumulation has been noted in other neurodegenerative disorders.¹⁵⁶ Among ALS patients, increased iron concentration has been reported in the ventral spinal cord¹⁵⁷ and in the motor cortex, especially the hand knob region, presumably corresponding to the small hand muscle weakness seen in these patients.¹⁵⁸

The potential role of the metalloids selenium has been investigated in endemic clusters of ALS in selenium-rich regions of South Dakota¹⁵⁹ and in Italy.¹⁶⁰ Recent studies of selenium in the CSF of patients in Italy have shown elevated selenite concentrations, maybe related to elevated selenium exposure via drinking water.¹⁶¹ To what extent these findings may be generalizable to other population remains to be elucidated.

Other metals with potential relevance for ALS are copper, aluminum, arsenic, cadmium, cobalt, zinc, vanadium, and uranium, all of which have been found in significantly elevated concentrations in the CSF of ALS patients when compared with healthy controls.¹⁶²

Pesticides

Pesticides are in widespread use worldwide and can be measured in various concentrations in air, food, and water. An association between pesticide use and ALS has been explicitly evaluated and suggested in previous studies,^{139–141,146,163–166} including two recent studies from India¹⁶⁷ and the USA (organochlorine compounds, pyrethroids, herbicides, and fumigants specifically).¹⁶⁸ In meta-analyses, pesticide use was found to be significantly associated with a higher risk of ALS,^{168,169} although the latter study¹⁶⁹ suggested a male-specific association.

β -methylamino-L-alanine

Exposure to β -methylamino-L-alanine (BMAA), an atypical amino acid, has been proposed to explain the high incidence of ALS-PDC in the western Pacific.⁴⁵ BMAA was originally believed to be produced on Guam and elsewhere by a local Micronesian plant, *Cycas micronesica*; more recently, it was recognized that BMAA does not originate from the plant itself but rather from cyanobacteria.¹⁷⁰ Further, cyanobacteria apparently produce BMAA in settings outside Guam.¹⁷⁰

In one study, BMAA was higher in the brain and spinal cord tissues of patients with ALS or Alzheimer's disease than in healthy controls or patients with other diseases.¹⁷¹ A recent study has demonstrated that BMAA bioaccumulates in the Baltic Sea ecosystem and identified pathways for human exposure.¹⁷² Neurotoxins other than BMAA produced by cyanobacteria may also contribute to neurodegeneration.¹⁷³

Viruses

Previous viral infection has also been considered as a potential risk factor for ALS. For example, a role of enteroviral infections in ALS has been hypothesized since neurons in the anterior horn of the spinal cord are the target cells both in ALS and enteroviral infections, including poliomyelitis.¹⁷⁴ Using reverse transcriptase (RT) in situ polymerase chain reaction, enterovirus RNA was detected in motor neurons of the anterior horn of patients with ALS.¹⁷⁵ Exposure to other viruses may also be important. Human herpesvirus (HHV)-6 seropositivity was associated with a more than threefold risk of ALS, and HHV-8 seropositivity with a more than eightfold risk.¹⁷⁶ Retroviruses, such as human immunodeficiency virus and human T-cell lymphotropic virus-1, caused motor neuron syndromes.¹⁷⁷ Some as yet unidentified retrovirus might also be a risk factor for ALS, because a mouse retrovirus (murine leukemia virus) causes both a lower motor neuron syndrome and leukemia/lymphoma.¹⁷⁸ A more broad measure of retroviral infection, ie, serum activity of reverse transcriptase (an enzyme characterizing retroviral infections), was similar among ALS patients and their blood relatives, but lower among their spouses, who had levels similar to that of other non-blood-related controls.¹⁷⁹ More recent studies of the expression of human endogenous retroviral sequences have revealed significantly increased expression of human endogenous retro virus type K (HERV-K), one of the two most studied human endogenous retroviruses given its complete open reading frame and ability to form virus-like particles, in the serum, muscle, and post mortem brain tissue of ALS patients.^{180–183}

Medical conditions

The general belief that ALS is a complex multifactorial disease has suggested the importance of studying the relationship between ALS and other medical conditions, which may share environmental risk factors or a genetic predisposition with ALS. In this review, we focus our discussion on the potential roles of head trauma, metabolic diseases, cancer, and neuroinflammation in ALS.

Head trauma

Early case-control studies reported a significant association between history of head trauma and ALS.¹⁸⁴ Aiming to rule out the possibilities of recall bias and reverse causality (ie, trauma as a result, rather than a cause, of ALS), later studies generally used more objective assessment of head trauma history and excluded traumas experienced during the years immediately before the diagnosis of ALS.^{185,186} Severe head traumas that were hospitalized were not associated with a higher risk of ALS in Sweden.¹⁸⁶ A possible association of ALS with milder head traumas, perhaps specifically with repeatedly experienced mild traumas, has not been thoroughly addressed.

Metabolic diseases

An interest in the relationship between metabolic disorders and ALS arose after the observation that ALS patients are hypermetabolic.¹⁸⁷ Previous studies suggested that type 2 diabetes is associated with a lower risk of ALS,¹⁸⁸ while type 1 diabetes, as well as some other autoimmune diseases, might instead be risk factors for ALS.¹⁸⁹ In a recent study, we confirmed an inverse association between type 2 diabetes and risk of ALS, and found that type 1 diabetes was indeed associated with a threefold risk of ALS.¹⁹⁰ Medications used for treatments of metabolic disorders, independently of the underlying disorders, may also be associated with the development of ALS. However, the evidence gathered to date is inconclusive regarding the relationship between use of statins¹⁹¹ and the risk or progression of ALS, and between the antidiabetic drug, pioglitazone, and progression of ALS.¹⁹² However, these findings are not surprising given the complexity of their properties. Pioglitazone, for example, is both antioxidant and anti-inflammatory and may protect against neurodegeneration, but it is also antidiabetic and antidyslipidemic and may therefore be detrimental for ALS, if the emerging evidence of a potentially protective effect of obesity and type 2 diabetes with regard to ALS proves true.

Cancer

Although the incidence of neurodegenerative diseases and of cancer increases in older adults, these two groups of diseases are characterized by largely opposing cellular behavior, ie, premature cell death in neurodegeneration and resistance to cell death in carcinogenesis.¹⁹³ A potential inverse relationship between neurodegenerative diseases (eg, Alzheimer's disease and Parkinson's disease) and cancer has been observed, and is plausible for the reasons discussed.¹⁹⁴ Based on clinical case series or case reports, earlier studies suggested a positive association between ALS and

cancer.^{195–197} Most epidemiological studies have refuted such a link in general,^{198–201} except for melanoma.^{199,201–203} The most recent, large-scale, prospective cohort studies have similarly refuted a positive association between cancer, including melanoma, and ALS.^{204,205}

Neuroinflammation

Since the earliest pathological changes in ALS appear to occur in axons, dendrites, and synapses,²⁰⁶ studies of the relationship between inflammatory conditions around the motor unit and ALS may shed light on the pathological development of ALS. Clinically, early symptoms of ALS can be difficult to differentiate from symptoms of other inflammatory neuromuscular diseases such as myositis, myasthenia gravis, Guillain–Barré syndrome, and multiple sclerosis. Due to the difficulties in determining the correct diagnosis, misdiagnosis may be an explanation for any higher-than-expected co-occurrence of ALS and inflammatory diseases.²⁰⁷ Interestingly, ALS and multiple sclerosis were reported to co-occur in individuals with the *C9ORF72* repeat expansion, suggesting some biological overlaps between ALS and autoimmune/inflammatory diseases.²⁰⁸ However, apart from several reports of cases diagnosed with both ALS and with some of the conditions above, few studies have addressed this issue.

Interactions between genetic and non-genetic factors

Intriguingly, studies have shown that even subjects carrying highly penetrant mutations do not always develop ALS. For example, based on a pair of monozygotic twins with a similar methylation level and repeat size of *C9ORF72* expansion but who were discordant for ALS, a recent study highlights the importance of non-genetic modifiers in the development of ALS.²⁰⁹ In that study, the co-twin who developed ALS had a history of both smoking and head trauma, whereas the non-ALS co-twin had neither exposure.²⁰⁹ Insight gained from studying gene-environment interactions has furthered our understanding of disease etiologies, for example, the interaction between the *APOE* gene and traumatic brain injury in Alzheimer's disease,²¹⁰ the *HLA* gene and smoking in multiple sclerosis,²¹¹ and the α -synuclein *Rep1* gene and Parkinson's disease.²¹²

Future developments

Identification of risk factors, especially non-genetic factors, for ALS has proven difficult, and likely reflects the complexity of the disease. Below, we briefly discuss reasons that in our opinion are the most important for the lack of success, and outline strategies to circumvent these obstacles.

Arguably, the most pressing unmet need in ALS research is to better classify subtypes of ALS, in terms of clinical presentation of symptoms, survival profile, genetic background, and underlying pathology.^{213,214} The lack of such information is likely to contribute to the inconclusive findings to date regarding risk factors and underlying mechanisms for ALS, as well as the lack of success in various clinical trials for ALS.

Up until now, different risk factors have mainly been studied independently of one another. An alternative strategy would be to study different prevailing hypotheses in concert, rather than individually. Such a strategy might prove more informative, perhaps enabling identification of common pathophysiological pathways leading to motor neuron degeneration. One approach would be intensive evaluation of multiple risk factors within clinical and population-based case-control studies of ALS, where many different types of information could be collected at the time of recruitment. Another strategy might be to study a population at high risk for ALS because of the presence of one or more risk factors, such as family members of ALS patients, and to evaluate other risk factors within this population. If information could be collected longitudinally and repeatedly in such a setting, it would have substantial potential to further our understanding of the synergistic activities of different factors in leading to a higher risk of neurodegeneration.

Even for an individual risk factor, a more systemic approach may be needed to understand the mechanisms linking the factor to ALS. In the case of lead, for example, an effort should be made to incorporate measurements of exposure in different body compartments, including blood, CSF, bone, and muscle. Contrasting lead levels in different compartments provides a better understanding of the dynamics of lead metabolism and the permeability of different barriers between the peripheral circulation and the central nervous system, including the blood-brain barrier and the blood-CSF barrier.²¹⁵ Given the fact that bone is by far the largest storage compartment for lead, bone metabolism parameters, such as bone resorption and bone formation, will be important to understand whether and how lead is associated with the risk of ALS.

Although many non-genetic risk factors have been described for ALS, their interaction with different genetic backgrounds relevant to ALS remains elusive. This is likely due to the fact that ALS is a rare disease and single-center studies usually lack sufficient statistical power to test for gene-environment interactions. The past decade and the coming years are an important time for ALS genetics, as several international consortia are being developed with large-scale and deep screening at both the genetic and epigenetic

levels.⁸⁹ Many of these consortia also plan to collect detailed information on environmental and lifestyle risk factors, aiming to uncover important gene-environment interactions in the etiopathogenesis of ALS. The importance of ensuring representativeness of the enrolled ALS patients, collecting uniform, standardized data across multiple countries, ALS registries, or clinics remains a challenge for such studies.

Finally, while the majority of the previous case-control studies of ALS have primarily used one specific group of controls, be it population-based controls, controls with other diseases, or convenience controls (ie, family members, friends, neighbors), it is perhaps advisable to recruit multiple groups of controls in future case-control studies of ALS. Enrollment of relatives (including blood-related and non-blood-related) of ALS patients and individuals with other neurological or neurodegenerative diseases, as well as population-based controls would be preferable, wherever it is possible and affordable.

Conclusion

Over the last two decades, a great deal of new knowledge has been gathered on ALS, especially in terms of its underlying genetics and potential mechanisms implied by these genetic findings. In contrast, although we generally agree that there is substantial impact of non-genetic factors on the etiology of ALS, so far little progress has been made in identifying these factors with some degree of certainty. An improved knowledge of non-genetic risk factors for ALS, hand-in-hand with our increasing knowledge of ALS genetics, should prove more fruitful in deciphering the causes of this devastating disease and eventually providing a cure.

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