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The disease intersection of susceptibility and exposure: Chemical exposures and neurodegenerative disease risk☆

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Abstract Alzheimer's disease, Parkinson's disease, and motor neuron disease, the most common of the late-life neurodegenerative disorders, are in most cases thought to have complex etiologies. Common features among these disorders include insidious onset, pathological findings of protein aggregates and selected neuronal degeneration, and resulting characteristic clinical syndromes. The number of elders in the United States, including aging veterans, is increasing. Investigation of causes and preventive interventions for neurodegenerative disorders is increasingly relevant. Recent epidemiological and laboratory studies suggest that exposures years or decades before diagnosis can trigger the processes that ultimately result in a neurodegenerative disease. If this is correct, preventive measures may be needed in midlife or earlier. This article will focus on putative risk factors relevant to military service. Published by Elsevier Inc. on behalf of The Alzheimer's Association.

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1. Introduction

Alzheimer's disease (AD), Parkinson's disease (PD), and motor neuron disease are the most common of the neurodegenerative disorders beginning in middle to late life. Each condition is believed to be complex in etiology, the combined result of environmental and genetic determinants, but few etiologic factors are known. In each disorder, degeneration affects selected neuronal populations, resulting in characteristic clinical syndromes. Symptom onset is gradual, with progressive worsening over years. Protein aggregation is a unifying pathologic feature, although the specific proteins (e.g., tau, alpha-synuclein, TDP-43) and the location of the protein aggregates vary [1]. Diagnosis is typically after the fifth decade, but the underlying disease process is thought to begin years before diagnosis. The number and proportion of elderly in the U.S. population is growing rapidly, including aging veterans, with attendant increases in the economic and societal costs of late-life neurodegenerative disorders. Investigation of causes and preventive interventions are thus increasingly relevant. Recent epidemiological and laboratory studies suggest that exposures years or decades before diagnosis can trigger the processes that ultimately result in a neurodegenerative disease. If this is correct, preventive measures may be needed in midlife or earlier.

In this article, we will focus on putative risk factors relevant to military service. Even though active-duty service personnel are not as overtly affected, the unknown prodromal phase of these neurodegenerative conditions suggests that active duty personnel may suffer decrements in physical and cognitive performance, particularly when exposed to known risk factors associated with development of these

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disorders. Because little work has focused on military personnel or veterans, most of the work discussed will be based on observations in civilian populations.

2. Alzheimer's disease

AD is the most common cause of dementia in late life. Recent prevalence estimates suggest that dementia affects about 6% of the North American population 60 years and older and 30% of those 85 years and older [2]. Information from the Department of Veteran's Affairs (VA) suggests that: "The estimated number of U.S. Department of Veterans Affairs (VA) patients with all types of dementia (prevalence) in 2014 is 262,899 and ranges from a low of 135,216 to a high of 390,567. The low and high values are estimated based on the lower and upper bounds of the 95% confidence interval of prevalence rates reported in the research. These numbers are based on national prevalence rates for all types of dementia, applied to the VA patient population estimates. The estimated number of VA patients with Alzheimer's type dementia (prevalence) in 2014 is 166,872 and ranges from a low of 65,663 to a high of 269,566. The low and high values are estimated based on the lower and upper bounds of the 95% confidence interval of prevalence rates reported in the research. These numbers are based on national prevalence rates for Alzheimer's dementia, applied to the VA patient population estimates."

Presently, there is no diagnostic test for AD so diagnosis depends on the recognition of acquired impairment in multiple cognitive domains, including memory, language, visuospatial ability, executive function, and mood, that is severe enough to interfere with social or occupational functioning. A prodromal phase is recognized called mild cognitive impairment where cognitive decline is present but not yet severe enough to cause functional impairment. Pathologic confirmation of AD relies on the presence of two features: amyloid plaques composed of extracellular aggregates of the protein amyloid and neurofibrillary tangles comprising intraneuronal deposits of the protein tau. Current thought hypothesizes that neuronal death in AD is related to toxic effects of amyloid. Genetic factors contributing to AD include mutations on a small number of genes that cause AD primarily in young-onset patients and risk genes such as the E4 allele of the Apo E gene that increases the risk of AD by three to 10 times [3]. Although age is the strongest risk factor for AD, modifiable risk factors have been identified that include head trauma, less physical activity, and cardiovascular risk factors such as hypertension, stroke, diabetes, cigarette smoking, and high cholesterol [3].

2.1. Pesticides

The association of chemical exposures and AD is not as well studied as other environmental risk factors, and results are often inconsistent. Occupational exposure to pesticides compared with unexposed was associated with a relative risk of developing AD in men of 2.29 (95% confidence interval [CI] = 1.02–5.630) in a cohort study of 1500 elderly participants living in southwest France. No association was found in women, probably because of pesticide application tasks being performed almost exclusively by men [4]. The Cache County, Utah, study also assessed occupational exposure to pesticides in general but added questions regarding exposure to specific compounds including organophosphates and organochlorines. More than 3000 participants free from dementia at baseline received follow-up cognitive screening at 3, 7, and 10 years; those with positive screens were examined for dementia. After adjustment for age, sex, education, baseline cognitive function, and apolipoprotein e4 (APOE) genotype the hazard ratio for developing AD was 1.42 (95% CI 1.06–1.91) for any pesticide exposure, 1.53 (95% CI 1.05–2.23) for organophosphates, and 1.49 (95% CI 0.99–2.24) for organochlorines [5]. In another study of more than 17,000 patients living in southern Spain, AD cases were identified from computerized hospital records. The prevalence of AD was twice as high in those living in areas with high pesticide exposure compared with areas of low exposure, and this effect remained significant after adjustment [6].

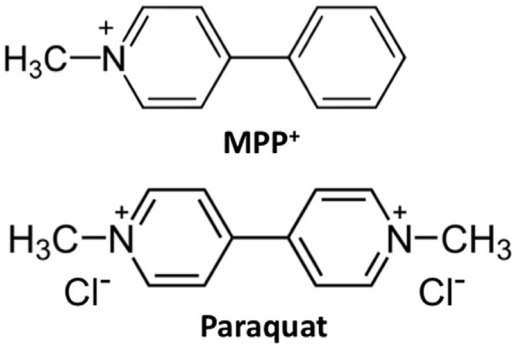

Fig. 1. MPP^+ and paraquat.

Owing to their persistence in the environment, organochlorines can be measured in body tissue years after exposure. Several studies have examined the association of serum levels of organochlorines and AD. In a recent case-control study from North India, mean levels of nine detected organochlorines were higher in 70 AD cases compared with 75 controls. Levels of three of these—B-HCH, dieldrin, and pp'-DDE—were significantly higher in cases [7]. Serum levels of

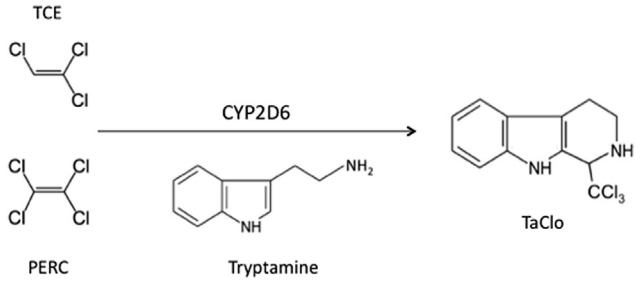

Fig. 2. Formation of TaClo from TCE and PERC. 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo) forms in the presence of tryptamine after cytochrome P450 2E1 (CYP2E1)-mediated oxidation of trichloroethylene (TCE) or tetrachloroethylene (perchloroethylene, PERC).

pp'DDE, but not B-HCH were significantly higher in 20 AD subjects compared with 50 Parkinson's disease patients and 43 normal controls in another case-control study [8].

Despite the fact that herbicides were used extensively during the Vietnam War, there are few studies of pesticide exposure and cognitive impairment or AD among veterans or active-duty military. More than 11 million gallons of the herbicide Agent Orange were sprayed over Vietnam between 1962 and 1971 to clear vegetation that could be used as cover by the enemy and to destroy food crops. The two constituents of Agent Orange—2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T)—as well as a 2,4,5-T contaminant, dioxin, have long been implicated in adverse health outcomes. The Air Force Health Study beginning in 1982 examined the association of Agent Orange exposure and health outcomes, including cognitive impairment. The cohort consisted of Air Force personnel exposed to Agent Orange through involvement in Operation Ranch Hand, the defoliant initiative in Vietnam, and an unexposed comparison group comprising personnel serving in other areas of Southeast Asia where Agent Orange was not used. Although global cognitive impairment among those with higher dioxin levels was not evident, there were lower scores on immediate and delayed recall as well as visuospatial memory in this group relative to the nonexposed comparison group. Differences were statistically significant, but small and of uncertain clinical significance [9]. Results were similar in the Vietnam Experience Study, in which neuropsychological performance was examined in veterans serving in Vietnam and veterans not serving in Vietnam. Overall neuropsychological functioning was similar between the two groups. Although Vietnam veterans had statistically significant lower scores on some tests of visual memory, visuospatial function, and abstract thinking, differences were small and of doubtful clinical relevance [10]. Last, another study found no association between an objective measure of Agent Orange exposure based on location of service and neuropsychological test scores [11]. For all of these studies, follow-up examinations are needed to assess these subjects later in life when cognitive problems typically become evident.

Supporting the need for additional studies is a recently conducted independent scientific review of Agent Orange and AD by the Institute of Medicine, National Academy of Sciences. The committee concluded that there was inadequate or insufficient evidence of an association between Agent Orange exposure and AD [12].

2.2. Solvents

Exposure to organic solvents and AD risk is less well studied. In one case-control study using incident cases of AD, exposure to one or more solvent groups was associated with an adjusted odds ratio (OR) of 2.3 (95% CI 1.1–4.7) [13]. However, occupational exposure to solvents was not associated with AD in a meta-analysis analyzing 11 case control studies [14].

2.3. Metals

The role of metals in AD has been considered since aluminum was found in high concentrations in brain regions with many neurofibrillary tangles from AD patients by Crapper and others in the early 1970s [15]. This was followed by the seminal work of Perl and Brody who found aluminum deposits in neurons bearing neurofibrillary tangles in the brains of AD patients, whereas no aluminum was found in healthy neurons [16]. Aluminum neurotoxicity has been demonstrated in animal models. Rats exposed to low-level aluminum ingestion develop severe cognitive impairment in old age, and aluminum accumulates in neurons of the hippocampal formation [17]. Epidemiological studies examining the association of aluminum exposure in water and diet have been mixed [18]. High aluminum content in water was associated with higher risk for cognitive decline and dementia in the prospective, population-based Personnes Agees QUID study [19]. Tea in particular has high levels of aluminum; however, several studies have shown no association of tea consumption with AD [20]. Similarly, another study examining the association of aluminum-containing antacids found no association [21]. Although the role of aluminum in the etiology of AD remains unsettled, experimental evidence and observational studies suggest an association between aluminum and AD exists.

Interest in the role of transition metals in the etiology of AD arises from the knowledge that excessive accumulations of copper, zinc, and iron can lead to increased oxidative stress and cytotoxicity. Some reports suggest these metals are concentrated in and around amyloid plaques in AD and may increase aggregation of amyloid [20,22]. However, many studies do not support these findings. In particular, a recent meta-analysis critically evaluated studies using accepted quantitative techniques to assess levels of copper, iron, and zinc in AD brains compared with similarly aged controls and found that levels of these metals were not elevated in AD brains. In view of these findings, the authors suggested that the hypothesis that oxidative injury in AD is related to transition metal excess should be reconsidered [23].

Lead has been linked to several adverse health outcomes, including cognitive impairment in children and adults, although studies examining the association of lead exposure with AD are few. Lead levels in the blood represent a measure of acute effects of recent lead exposure, whereas bone levels represent cumulative lead burden over years [24]. For example, bone lead but not blood lead has been associated with cognitive decline in a nonoccupational cohort of participants in the Veterans Affairs Normative Aging Study with the visuospatial/visuomotor domain being the most severely affected [25], suggesting that low-level cumulative exposure impairs cognitive function, and visuospatial function in particular. Interestingly, the susceptibility to effects on cognitive function related to cumulative lead exposure

may be modified by APOE genotype. The E4 allele of the APOE gene is a firmly established risk factor for AD. Presence of at least one E4 allele compared with not having E4 was associated with a worsening of the adverse effect of bone lead on neurobehavioral test scores among participants occupationally exposed to lead [26].

2.4. TBI

Individuals with traumatic brain injury (TBI) are at higher risk of dementia [27]. As discussed previously for PD, the VA has recently determined a secondary service connection for dementias of the following types: presenile dementia of the Alzheimer type, frontotemporal dementia, and dementia with Lewy bodies, if manifest within 15 years after moderate or severe TBI (*Federal Register* 2013-29,911, 38 CFR Part 3, Docket ID: VA-2012-VBA-0029, pages 76196-76209.)

3. Parkinson's disease

PD is a chronic, progressive neurodegenerative disease of aging characterized clinically by the classical motor signs of parkinsonism (resting tremor, bradykinesia, cogwheel rigidity, postural reflex impairment) and a variable constellation of associated features including autonomic, sensory, cognitive, and psychiatric changes. These clinical features correspond to the anatomic distribution of pathologic changes, consisting of neuronal degeneration and commonly aggregation of the protein alpha-synuclein in specific neuronal populations, including the substantia nigra, locus ceruleus, other brainstem and cortical regions, and the peripheral autonomic nervous system. A prodromal period lasting many years precedes the onset of motor parkinsonism in many, if not all, cases. Prodromal features preceding motor parkinsonism may include constipation, hyposmia, rapid eye movement sleep behavior disorder, reduced heart rate variability, anxiety and depression.

As many as 1.5 million people in the United States currently suffer from the disease, with an estimated 70,000 newly diagnosed cases per year. Men are more commonly affected. Incidence increases with age, and onset before age 50 is uncommon. The official number of individuals with PD currently treated in the VA is not available. However, an informal estimate is approximately 80,000 PD patients (http://www.parkinsons.va.gov). These estimates do not include veterans receiving care from other providers.

3.1. Genetics

Parkinsonism can be caused by genetic mutations, but these inherited forms make up a small proportion of disease. Studies in World War II veteran twins and other twin populations found low concordance for PD, suggesting that environmental causes are important for most people with PD [28,29]. The most common genetic form of PD, PARK8, causes about 2% of PD cases in the United States [30]. Penetrance is incomplete in this dominantly inherited parkinsonism, and environmental or other genetic factors determine whether PD will occur in carriers. Common genetic variation also causes small increases in PD risk, typically 10%–15% [31]. The interaction of environmental exposure and genetic variation (gene–environment interaction) likely cause most cases of PD.

3.2. Environmental modifiers

Interest in environmental causes of PD was sparked when the chemical MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) (Fig. 1) was identified as the cause of human parkinsonism clinically similar to PD [32]. Laboratory studies showed that MPTP enters the brain via the large neutral amino acid transporter and is metabolized to a reactive compound that specifically blocks mitochondrial complex I, causing experimental parkinsonism [33–37]. These observations provided biologic plausibility to the hypothesis that environmental chemical exposure could cause PD.

3.3. Pesticides

Because MPTP resembles the herbicide paraquat (1,1′-dimethyl-4,4′-bypyridinium dichloride) (Fig. 1) structurally and the insecticide rotenone functionally and because several ecologic studies suggested a rural preponderance of PD, pesticides and other factors associated with the rural environment were among the earliest chemical exposures investigated [38]. An association between pesticide exposure and PD has been confirmed based on more than 80 populations studied [39]. The term *pesticide* includes herbicides, insecticides, fungicides, and rodenticides, and represents hundreds of chemicals with widely different structures and biologic effects. Identifying specific chemicals is important to understanding disease pathogenesis, yet few studies investigated specific compounds. Studies that exist suggest that, in addition to direct toxic effects pesticides may have, susceptibility to PD from pesticides may occur through modification of genes for detoxifying enzymes. An example is a recent study indicating that alterations in neuronal aldehyde dehydrogenase enzymes are associated with increased risk for development of PD [40].

The pesticide most frequently associated with PD is paraquat, a commonly used herbicide with a structure similar to MPTP [39]. Occupational paraquat exposure is associated with more than double the risk of PD, and even "passive" exposure through having a residence near treated fields can increase risk, particularly when combined with the fungicide maneb [41–43]. Persons with an inactive variant of the gene encoding the detoxifying enzyme glutathione-S-transferase T1 have an 11 times greater risk of PD when exposed to paraquat than do those with a functional version of this gene [44]. In laboratory studies, paraquat causes increased production of reactive oxygen species, alpha-synuclein aggregation,

and selective nigral injury [45–48]. Paraquat has been used as a defoliant in military operations.

A second herbicide, the organochlorine 2, 4-dichlorophenoxyacetic acid (2,4-D), was also associated with more than double the risk of PD in one study [41] but not others [49,50]. 2,4-D is a component of Agent Orange, a tactical herbicide mixture used in Vietnam and recently determined to be a presumptive cause for PD in military veterans [51]. The organochlorine dieldrin was shown to be elevated in brains and serum of PD cases [52–54]. In the laboratory, dieldrin causes alpha-synuclein fibrillary aggregation, depletes dopamine, and causes oxidative stress. Other organochlorine pesticides found at higher levels in brain or serum of PD cases are lindane and beta-hexachlorocyclohexane [8,52], but these compounds have not been associated with increased risk in epidemiologic studies and specific military uses have not been reported. Organochlorine toxicity may be greater in persons with genetically determined low activity of metabolizing enzymes, including ABCB1 and cytochrome P450 2D6 [55,56]. Occupational exposure to permethrin, an insecticide that blocks mitochondrial complex I and causes oxidative stress, tripled the risk of PD in one study [41], but the effect was less marked in another [57]. Animal studies of permethrin indicate that exposure to permethrin upregulated the vesicular monoamine transporter and the dopamine transporter (DAT) as well as enhancing physical activity [58,59]. Because the metabolic product of MPTP metabolism (MPP+) uses DAT to gain entry to dopaminergic neurons, permethrin may enhance risk in environments where other chemicals capable of entry through the DAT exist. Military use of permethrin- or lindane-permeated uniforms and equipment is common where malaria is endemic (http://www.publichealth.va.gov/exposures/gulfwar/pesticides.asp). A recent study concluded "that wearing permethrin-treated clothing does increase absorbed, internal dose levels of permethrin above population levels and is significantly related to wear-time duration" [60]. Permethrin is considered safe and protective in military use but is used with caution in specific military subpopulations (http://phc.amedd.army.mil/topics/healthyliving/wh/Pages/Women'sHealthPortal-Pregnancy.aspx) [61]. Organophosphate insecticides act as cholinesterase inhibitors, and are commonly used to control insect disease vectors and pests. With repeated exposure, noncholinergic effects including disrupted axonal transport, neurotrophin function, mitochondrial complex I inhibition, and oxidative stress may occur [62]. Exposure to methylparathion [57] and chlorpyrifos [63] has been associated with increased PD risk, but evidence is weak. Military exposure to cholinesterase inhibitor pesticides for pest control or chemical warfare and concurrent prophylaxis with pyridostigmine has been proposed, but not proven, to contribute to the syndrome of neurological and somatic symptoms constituting the Gulf War Syndrome [62,64]. Other pesticides blocking mitochondrial complex I, including rotenone, also more than double the risk of PD. Inferred residential exposure to the dithiocarbamate fungicides maneb, ziram, and zineb was associated with increased PD risk in studies in the California Central Valley and adverse effects may increase when combined with paraquat [42,43,63]. These chemicals cause oxidative stress and proteasomal dysfunction in experimental models, along with injury to dopaminergic neurons [65]. Apart from tactical use of pesticides, pesticides are used on bases or in combat settings to control insects and plant overgrowth.

3.4. Solvents

Occupational exposure to chlorinated solvents is also associated with an increased risk of PD [66,67]. In a study of World War II veteran twins, PD risk was more than six times greater in the twin exposed to trichloroethylene, TCE, and nearly significant increases were noted for perchloroethylene (PERC; OR: 10.5, CI: 0.97-113), and carbon tetrachloride (OR: 2.3, 95% CI: 0.9-6.1) [67] (Fig. 2).

TCE causes experimental parkinsonism in rats, producing reactive microglia, mitochondrial complex I inhibition, oxidative stress, alpha-synuclein aggregation, and degeneration of dopaminergic neurons. These chemicals are commonly used in military and civilian settings as cleaners, degreasers, and, in the past, skin disinfectants (http://www.publichealth.va.gov/exposures/solvents/index.asp). These solvents are environmentally persistent, and nonoccupational exposure may occur. For example, residential drinking water systems at Camp Lejeune were contaminated with chemicals, including PERC and TCE, between 1957 and 1985. To date, no adverse health effects have been associated with this exposure [68] (http://www.publichealth.va.gov/exposures/camp-lejeune/research.asp).

3.5. Polychlorinated biphenyls

Evidence supporting a relationship between polychlorinated biphenyl (PCB) exposure and PD is inconsistent. Women, but not men, occupationally exposed to PCBs were more likely to die from PD [69], and women with higher serum PCB levels were more likely to show imaging evidence of reduced striatal dopamine transporter density [70]. In postmortem studies, PCBs were higher in striatum of PD cases than controls [71] However, in a prospective study of Finnish workers, serum PCB levels were not higher in workers who developed PD [72]. In animal models, PCB exposure is associated with relatively selective, persistent, reduction of dopamine, primarily affecting caudate, putamen, substantia nigra, and olfactory tract [73–76]. PCBs persist in soil, water, and air, and tend to concentrate in animals higher on the food chain. Dietary PCB intake has been suggested as a cause of excess of PD in Greenland [77]. PCBs were used extensively as coolants and lubricants before a 1977 ban. Veterans who worked on repair and maintenance of transformers, capacitors, and conduits before 1977 may have been exposed during military service (http://www.publichealth.va.gov/exposures/pcb/index.asp).

3.6. Other chemical exposures

Exposure to various metals, including manganese, iron, and lead, has long been suggested to increase risk of PD, based on experimental in vitro and in vivo studies, but human evidence remains inconclusive [78–80].

3.7. Particulate matter

Ambient total suspended particles from traffic have been associated with an increased risk of PD [81]. Postmortem comparison of brains from persons living in high and low air pollution environments found ultrafine particulate matter in the olfactory bulbs and immunoreactivity to beta amyloid bA42 and/or alpha-synuclein in neurons, glial cells, and/or blood vessels of those living in high, but not low, pollution areas [82], and pollution-induced inflammatory brain mechanisms, suggesting that air pollution may be involved in the development of PE and/or dementia. Veterans deployed to polluted or dusty environments, such as the Persian Gulf or Afghanistan, may be at risk for particulate matter exposure, although to date increased mortality from PD has not been observed [83] (http://www.publichealth.va.gov/exposures/sand-dust-particulates/index.asp).

3.8. TBI

Mild to moderate head injury, typically occurring decades before PD onset, has been associated with increased risk of PD in the majority of published studies [84] and risk increases with the number of injuries [85–88]. There is evidence for gene–environment interaction. PD risk is tripled in those with a long Rep1 variant in the alpha-synuclein gene (OR 3.5, 95% CI 1.4–9.2, p-interaction 0.02), and age at disease onset is nearly 5 years earlier in those with both head injury and the gene variant [89]. TBI can cause disruption of blood brain barrier, increasing central nervous system passage of toxicants, can trigger inflammatory processes, interfere with axonal transport, and induce aggregation of alpha-synuclein and tau proteins, all processes that may ultimately lead to neurodegenerative changes [90]. TBI may occur during military service as the result of blast injuries, vehicle crashes, falls, or other injuries. About 90% of head injuries during military service are mild (http://www.publichealth.va.gov/exposures/traumatic-brain-injury.asp). An estimated 285,000 Iraq and Afghanistan veterans have been diagnosed with TBI as of 2008. The VA has published a new regulation, effective in early 2014, providing for the consideration of PD and certain dementing disorders because service-related disabilities in veterans with moderate to severe service-related TBI (*Federal Register* 2013-29,911, 38 CFR Part 3, Docket ID: VA-2012-VBA-0029, pages 76196-76209.)

3.9. Other modifiable risk factors

Although the focus of this review is on military-associated chemical exposures, it is important to mention that many other factors have been associated with PD, notably behavioral and lifestyle factors [91]. Those of possible military relevance are mentioned here. A consistent inverse association between tobacco use and PD was first noted in the VA population [92,93] and subsequently replicated in nearly every population studied worldwide [94,95], including World War II veteran male twin pairs discordant for PD [96], suggesting that some component of tobacco, possibly nicotine, may protect against the development of PD [97]. Caffeine use has also been inversely associated with PD in several populations, especially in men [98,99]. Preliminary reports suggest that physical activity and certain dietary factors may lower PD risk [100,101], whereas shift work may increase risk [102]. Prisoner of war status has been associated with increased PD risk [103,104], but this is controversial [105]. Because PD likely is determined by the combination of risk and protective factors plus genetic predisposition, awareness of these additional determinants can be important in planning interventions for disease prevention as well as investigating etiology.

4. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder of motor neurons that typically results in death from respiratory failure within 3 years of diagnosis. Although primary symptoms result from degeneration of upper and lower motor neurons, ALS is a multisystem disorder that widely affects non-motor neurons. At least half of affected individuals manifest some degree of executive dysfunction and other cognitive impairment, and 14% have frank frontotemporal dementia (FTD) [106]. ALS is clinically and pathologically pleiotropic and constitutes a syndrome of diseases with likely diverse etiology [107]. Incidence increases from 2/100,000 at age 50 to 15/100,000 by age 75 [108,109]. Rates are similar in Europe, North America, and Japan, but may be lower in China [110], possibly reflecting its relatively recent industrialization. Increasing incidence over time could also implicate environmental factors related to industrialization. This is supported by several recent studies. Fang et al. found a 30% increased incidence from 1991 to 2005 in Sweden [108], and Murphy et al. observed a doubling of incidence in New Zealand from 1985 to 2006 [111]. Other recent studies found birth cohort components suggesting the introduction of an environmental risk factor during the early part of the 20th century [112,113]. Incidence in men is 30%–50% greater than in women, a difference that has narrowed in more recent studies, possibly reflecting increasing similarity of environmental risk factor exposures [109,112,113].

Approximately 90% of ALS is sporadic and 10% familial, although this designation may result in substantial misclassification [114]. A genetic basis has been identified for approximately 60% of familial cases and 10% of

sporadic [115]. The most common point mutated genes include *SOD1* (Cu/Zn superoxide dismutase), *FUS* (fused in sarcoma), and *TARDBP* (TDP-43). A recently discovered noncoding expansion of a hexanucleotide sequence in *C9orf72* is the most common genetic cause of both familial (~40%) and sporadic (~6%) ALS, and is also a primary cause of frontotemporal dementia [116]. ALS etiopathologic processes involve oxidative and nitrative damage, microglial activation/inflammation, mitochondrial dysfunction, protein aggregation (e.g., TDP-43), impaired axonal transport, apoptosis, growth factor alterations, glutamate excitotoxicity, and dysregulated RNA metabolism (reviewed by Rothstein [117]). Importantly, different risk factors may affect disease initiation and propagation.

4.1. β-*N*-Methylamino-L-alanine (BMAA)

The environmental hypothesis of ALS derives in part from the observation 60 years ago that rates of ALS were 100-fold higher among the indigenous Chamorro people of the south Pacific island of Guam [118]. During the ensuing decades, there has been a dramatic decline in incidence, strongly suggesting a reduction in exposure to one or more causative environmental agents, possibly of a chemical or infectious nature. BMAA is a non-protein amino acid produced by ubiquitous cyanobacteria, which has been suspected as the environmental agent responsible for the Guamanian ALS cluster. BMAA is a glutamate receptor agonist that depletes glutathione and may enhance protein aggregation [119]. The BMAA hypothesis was initially based on the observation that it was present in flour made from the seed of the cycad plant *Cycas micronesica,* which was a dietary staple of the Guamanian Chamorro people [120]. Although its concentration in cycad flour is too low to cause toxicity [121], BMAA is bioconcentrated by fruit bats (flying foxes) and other animals whose consumption may result in very large exposures [122,123]. The hypothesis gained support when BMAA was found in brains of Chamorros who died from ALS, but was not detected in normal control brains [124]. In a larger follow-up study, this same research group detected BMAA in protein-bound fractions of brain tissue from U.S. patients with sporadic ALS or AD, but not in normal controls or in Huntington's disease [125]. However, other investigators using different analytic methods failed to detect BMAA in brain from Chamorros with ALS or patients with AD, casting doubt on the association [126,127].

Of particular relevance to the putative ALS cluster in Gulf War veterans (see the following section), desert dust in Qatar was found to contain cyanobacteria and associated neurotoxins including BMAA and its isomer 2,4 diaminobutyric acid. The authors propose that physical disturbance of the soil, such as through seasonal rains and/or vehicular traffic, could aerosolize cyanotoxins and lead to substantial inhalation [128]. A possible relationship to BMAA has also been proposed in a New Hampshire cluster where a 10- to 25-fold higher than expected incidence of ALS occurred among residents living near a small lake with frequent cyanobacterial blooms [129].

Motor neurons are particularly sensitive to BMAA toxicity [130], and animal models manifest some of the motor deficits seen in ALS as well as evidence of mitochondrial disruption and increases in TDP-43 protein [131,132]. However, other animal models do not replicate ALS pathology, and BMAA toxicity is very low in cellular models [118]. Although relatively high concentrations of BMAA are required to cause toxicity in cellular and animal models, synergism with other toxicants such as methylmercury has been reported [133].

4.2. Gulf war

Several studies assessed the rate of ALS associated with military service in the 1991 Gulf War. This research was spurred by reports of a large number of young service members with ALS. Haley identified cases of ALS between 1991 and 1998 from military registries and a publicity campaign, and found 17 affected Gulf War veterans younger than age 45. The observed incidence equaled the expected incidence from 1991 to 1994, but increased to two- or three-fold the expected incidence after 1995 [134]. Horner et al attempted to ascertain all ALS cases by the end of 1999 among individuals on active duty August 1990 through July 1991. Personnel deployed to the Gulf Region were considered "exposed," and those not deployed to the Gulf were considered "unexposed." They identified 107 cases among 2.5 million personnel, and found a doubling of risk associated with deployment to the Gulf (relative risk [RR] 1.9, 95%CI 1.3–2.8); risk was highest for deployed Air Force personnel (RR 2.7, 95%CI 1.2–5.8) [135]. In contrast, a study of Gulf War veteran mortality through 2004 found no excess frequency of ALS [83]. Horner et al. suggest that the increased rate of ALS was a time-limited outbreak that peaked in 1996 and declined thereafter [136].

No specific environmental factors have been linked to Gulf War service, but Miranda et al. used a geographic information system analysis to identify specific service locations within the Gulf associated with subsequent ALS [137]. Risk was higher in proximity to chemical weapons facilities at Khamisiyah, Iraq, as well as several other specific locations where unknown environmental exposures may have occurred. However, in the 1.2 million member American Cancer Society Cancer Prevention Study II prospective cohort, ALS mortality was increased with any military service, and not specifically Gulf War service [138], consistent with a common environmental exposure associated with military service in general. Based on the epidemiologic data and a summary report by the Institute of Medicine [139], the VA presumes ALS diagnosed in all veterans is related to their service, irrespective of period of service.

4.3. Lead

The neurotoxic properties of lead have been recognized for centuries. Lead is a pro-oxidant, stimulates protein aggregation, disrupts glutamatergic signaling, and alters neuronal growth factors [140]. It is of particular interest to the military because of the possibility of exposure through a range of activities including weapons emissions and lead paint. Lead is one of the most extensively studied environmental risk factors in ALS, with reported associations as early as 1850 [141]. Numerous studies of widely varying quality have been conducted, most of which found at least a doubling of risk of ALS (reviewed elsewhere [142,143]). Bone lead reflects cumulative exposures (trabecular bone half-life 3–5 years, cortical bone half-life 15–25 years) [144], and it avoids possible recall bias of historical studies. Kamel et al. found a dose-dependent increased risk of ALS associated with both patellar and tibial lead, with a 2.3- to 3.6-fold increase for each doubling of bone lead [145]. In a large population of U.S. military veterans, the same group assessed blood lead levels while adjusting analyses for measures of bone turnover. A doubling of blood lead was associated with a 1.9-fold adjusted risk of ALS [146]. Interestingly, a doubling of risk was also associated with a polymorphism in the *ALAD* gene encoding the lead-binding protein d-aminolevulinic acid dehydratase that enhances binding affinity [142].

4.4. Other metals

Like lead, mercury is a well-recognized neurotoxin, and a mechanistic link to ALS is plausible. Case reports of ALS after acute mercury intoxication have been described (reviewed in [143]). Though limited data exist, epidemiologic studies provide little to no support of an association with ALS [145,147–149]. However, mercury hastens the development of the ALS phenotype in an *SOD1* mutant mouse model [150], and further research into possible genetic and environmental interactions is warranted. Selenium is both a pro- and antioxidant and is a potential neurotoxin [151]. High levels of environmental selenium was associated with a cluster of ALS [152], and ALS incidence was markedly elevated in association with high selenium levels in drinking water [153,154], but tissue-based studies have been mostly negative [155,156].

4.5. Pesticides

At least a dozen studies have investigated associations of pesticide exposure and ALS risk [148,149,157–162]. Although not all were statistically significant, every study with at least five exposed subjects reported an increased risk of ALS, with ORs ranging from 1.4 to 6.5. In addition, other studies found an increased risk associated with agricultural work [163–165]. McGuire et al. conducted a high-quality population-based study of 174 incident cases and 348 well-matched controls in Washington state [148]. Industrial hygienists (IH) unaware of disease status estimated exposures by review of lifetime occupational history questionnaires. In men, ever-exposure to agricultural chemicals (pesticides and fertilizers) was significantly associated with ALS (OR 2.8, 95%CI 1.2–4.8), and risk was similarly increased for exposure to insecticides. Importantly, a dose-response relationship was seen, with an OR of 1.6 for low exposure to pesticides (relative to no exposure) and 3.3 for high exposure (P for trend = 0.02). In the only prospective cohort study of pesticides and ALS, self-reported regular pesticide exposure at study baseline was not associated with mortality from ALS (RR 1.1, 95%CI 0.8–1.4), although risk was modestly elevated (RR 1.4, 95%CI 0.9–2.3) when subjects with incomplete exposure data were excluded [160].

Only a single study assessed exposure to specific agents. Kamel et al. [161] studied a large cohort of professional pesticide applicators, a highly exposed population with good recall of the specific chemicals they used. Forty-one cases with ALS determined through death records were compared with the 84,698 cohort members without ALS. ALS risk tended toward significance for ever use of organochlorine insecticides (OR 1.6, 95%CI 0.8–3.5), pyrethroids (OR 1.4, 95%CI 0.6–3.4), herbicides (OR 1.6, 95%CI 0.7–3.7), and fumigants (OR 1.8, 95%CI 0.8–3.9). Although no specific agent was significantly associated, risk was consistently elevated for individual organochlorine insecticides including aldrin (OR 2.1, 95%CI 0.8–5.1), dieldrin (OR 2.6, 95%CI 0.9–7.3), DDT (OR 2.1, 95%CI 0.9–5.0), and toxaphene (OR 2.0, 95%CI 0.8–4.9).

Two recent independent meta-analyses of studies of pesticides and ALS both found summary risk ratios of 1.9 with minimal between-study heterogeneity [141,161]. Thus, the totality of epidemiologic evidence provides good support for an association of pesticides and ALS. Military aspects of pesticide use are discussed previously in the PD and AD sections.

4.6. Solvents

Solvent exposure can cause oxidative stress, mitochondrial toxicity and protein aggregation, and damage the cytoskeleton of long axons, resulting in a polyneuropathy [166]. Solvents are commonly used by military service members in a wide variety of settings for purposes such as cleaning, degreasing, and painting, and some agents are common groundwater contaminants. Numerous studies over several decades have assessed the association of solvents and ALS, with many finding an increased risk associated with self-reported solvent exposures [157–159,165] and/or occupations with likely exposure, such as carpenters, painters, construction workers, or leather workers [147,164,167]. However, others found no association with solvents [149,162,168], and in the large prospective American Cancer Society Cancer Prevention Study II prospective cohort mortality study, risk was not increased for those endorsing the use of chemicals/acids/solvents

[160]. As with pesticides, however, most studies evaluated solvents as a general class, rather than specific agents. In contrast, McGuire et al. assessed specific agents in their Washington state case control study described previously [148]. IH-determined risk was significantly elevated for solvent classes including alcohols/ketones (OR 2.0, 95%CI 1.0–4.0) and degreasers (OR 1.9, 95%CI 1.1–3.3), and was near-significant for benzene, toluene, or xylene. Specific agents were also assessed by Fang et al. using IH review of occupational histories [147]. Many solvent chemicals were associated with ALS risk—predominantly in nonsmokers. These included acetone (OR 2.5, 95%CI 1.0–6.3), aliphatic chlorinated hydrocarbons (OR 4.1, 95%CI 1.6–8.9), glycol ethers (OR 5.1, 95%CI 1.9–13.7), n-hexane (OR 3.4, 95%CI 1.3–9.6), and xylene (OR 3.1, 95%CI 1.2–8.1). The authors propose that smoking may reduce the toxicity of these agents via induction of metabolic enzymes.

4.7. Formaldehyde

Formaldehyde gas may be emitted from plywood building materials or from insulation, glues, or paints, and has been identified as a cause of health complaints among deployed personnel at bases in Iraq and Afghanistan. (http://phc.amedd.army.mil/PHC%20Resource%20Library/Formaldehyde%20FS%2055-012-1011.pdf) Self-reported exposure to formaldehyde at study baseline was associated with an increased risk of subsequent ALS mortality in the prospective ACS-II study (RR 2.5, 95%CI 1.6–3.9), with a strong dose-response relationship for years of use ($P = .0004$) [160]. In a high-quality case control study that used IH estimates of cumulative lifetime exposure, formaldehyde was not associated with ALS, except in those with the very highest cumulative exposures. Risk was increased threefold in those with greater than 60,000 lifetime hours of exposure [147]. Possible toxic mechanisms include inhibition of superoxide dismutase and mitochondrial damage [169].

Smoking has been associated with increased risk of ALS in several rigorous studies [170–172], but others, including a large prospective Swedish cohort [173] found no association (reviewed in [174]). A meta-analysis that pooled results of five large prospective cohorts found significantly increased risk in both men and women smokers (RR 1.4, 95%CI 1.1–1.9), as well as a suggestion of a dose response, and increased risk associated with initiating smoking at a younger age [175]. Proposed mechanisms include oxidative stress, combustion-generated formaldehyde, and effects on vascular endothelial growth factor [160,176].

4.8. Future directions

PD, AD, and ALS often have overlapping clinical syndromes. Certain chemical exposures and TBI are associated with increased risk of any of the three disorders, suggesting a common mechanism of injury among the late-life neurodegenerative disorders. Phenotypic expression after a chemical insult or TBI may be the result of multiple factors, including genetically determined vulnerabilities and other beneficial or harmful environmental conditions. Shared clinical features and risk profiles suggest that screening for multiple neurodegenerative disorders simultaneously may be the most efficient approach. In some cases, preventive interventions may also be useful for more than one of these neurodegenerative disorders. Identification of risk factors and interventions in veteran populations may ultimately lead to the development of effective interventions to protect active military personnel from future neurodegenerative disease.

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