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Linking pesticide exposure and dementia: What is the evidence?

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ABSTRACT

There has been a steep increase in the prevalence of dementia in recent decades, which has roughly followed an increase in pesticide use some decades earlier, a time when it is probable that current dementia patients could have been exposed to pesticides. This raises the question whether pesticides contribute to dementia pathogenesis. Indeed, many studies have found increased prevalence of cognitive, behavioral and psychomotor dysfunction in individuals chronically exposed to pesticides. Furthermore, evidence from recent studies shows a possible association between chronic pesticide exposure and an increased prevalence of dementia, including Alzheimer's disease (AD) dementia. At the cellular and molecular level, the mechanism of action of many classes of pesticides suggests that these compounds could be, at least partly, accountable for the neurodegeneration accompanying AD and other dementias. For example, organophosphates, which inhibit acetylcholinesterase as do the drugs used in treating AD symptoms, have also been shown to lead to microtubule derangements and tau hyperphosphorylation, a hallmark of AD. This emerging association is of considerable public health importance, given the increasing dementia prevalence and pesticide use. Here we review the epidemiological links between dementia and pesticide exposure and discuss the possible pathophysiological mechanisms and clinical implications of this association.

1. Introduction

Dementia, and in particular its commonest form, Alzheimer's disease (AD), constitutes a major health problem, being associated with significant morbidity and mortality (Ballard et al., 2011). Consequently, the financial and emotional burden of dementia is enormous, both at the level of the individual and his/her caregivers and at the level of the society at large (Jonsson and Wimo, 2009). Furthermore, there has been a worrisome steep increase of dementia prevalence in recent decades and this trend, given the aging population in Western and other countries, such as China and India, is expected to continue in the forthcoming years (Ballard et al., 2011).

This major health impact of dementia has instigated multiple studies on possible etiological factors accounting for the onset and progression of dementing illnesses. The vast majority of dementia cases occur in the elderly, making age the most important, but non-modifiable risk factor. Genetic factors have been estimated to account for up to 70% of the risk associated with AD; other risk factors include obesity, smoking, lack of exercise, mid-life hypertension and diabetes (Ballard et al., 2011). Special interest has focused on environmental factors of rising importance that could parallel the rising prevalence of dementia. Much work has been focused on exposure to toxic metals such as copper, aluminum and lead, the latter receiving special attention because of the possibility that exposures in early development may influence neurodegenerative disease in later life (Cannon and Greenamyre, 2011). In contrast, exposure to pesticides has received comparatively little attention with regard to their possible role in dementia. Pesticides are used in agriculture, farming or other applications for protecting humans from the damaging effects of pests (Sanborn et al., 2007; Hernández et al., in press). Target pests for pesticides include insects, weeds, animals, birds, nematodes and microorganisms, that produce harm to humans either directly or indirectly (e.g. by reducing the production and quality of an agricultural exploitation or by the spread of disease).

The nature of pesticides, that is to control living species, is at the heart of their potential toxicity to humans. Furthermore, the fact that they need to be deliberately spread to the environment to reach their targets leads to inadvertent exposure of most of the

Abbreviations: AD, Alzheimer's disease; FTD, frontotemporal dementia; HR, hazard ratio; LBD, Lewy-body dementia; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; PD, Parkinson's disease.

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human population. The toxicity of pesticides can often cross species barriers and inflict damage to many species, including humans. Specifically, many pesticides, in particular insecticides, are neurotoxic (Bjørling-Poulsen et al., 2008). Acute toxic effects are well known, but uncertainties still remain regarding chronic and long term effects, including their effect on the pathogenesis of cancer, dementia (including AD dementia), Parkinson's disease (PD) and other devastating disorders (Gilden et al., 2010).

It has been repeatedly reported that acute high-level exposure to certain pesticides has significant neurotoxic effects (Costa et al., 2008). These acute effects of pesticides depend on the nature of the pesticide, the route of exposure, the amount of pesticide absorbed and the time frame within which this exposure took effect. A well-known example of the acute effect of pesticides is the acute inhibition of the enzyme acetylcholinesterase in organophosphate poisoning, which presents with muscle weakness, convulsions, respiratory and circulatory problems, ataxia, tremor, salivation, lacrimation, miosis, sweating, diarrhea and urinary incontinence (Aygun, 2004).

Chronic exposure to pesticides has also been associated with a variety of neurological disorders, the most well-known example being the possible association between PD and pesticide exposure (Brown et al., 2006; Tsatsakis et al., 2008; Moretto and Colosio, 2011; Freire and Koifman, 2012; Tsatsakis et al., 2012a). Other neurological diseases possibly associated with chronic pesticide exposure include amyotrophic lateral sclerosis and peripheral polyneuropathy (Sanborn et al., 2007; Costa et al., 2008; Gilden et al., 2010; Kanavouras et al., 2011; Kamel et al., 2012).

In addition, there is evidence of increased prevalence of cognitive, behavioral and psychomotor dysfunction in individuals chronically exposed to pesticides (Bosma et al., 2000). A possible link of chronic pesticide exposure to increased prevalence of dementia, including its commonest form, AD would raise considerable public health concern, given the ever increasing dementia prevalence and the widespread pesticide use. Here we review the epidemiological links between dementia and pesticide exposure and discuss the possible pathophysiological mechanisms and clinical implications of this association.

2. Information from epidemiological and other clinical studies

2.1. Introduction to the methodology of the studies and their limitations

The key issue in any toxicological epidemiological study is collection of sound and adequate data on the levels of exposure of the individuals under investigation. Epidemiological studies are sometimes retrospective, and retrospective exposure assessment is very often a challenge. This is especially true in the field of pesticides, where intermittent exposure, non-continuous use of variable mixtures of active ingredients and intraseasonal variability of the active ingredients used make the identification of the source of exposure extremely difficult. This means that instead of exposure data, different crude proxies of exposure are used, for example "having been in the past an agricultural worker" or even "having been a rural area dweller". Other proxies of exposure can be "having been a pesticide applicator" or only "having used personal protective devices". Thus, the high risk of recall bias or/and misclassification in exposure subgroups is obvious. In light of these, it is often practically impossible to define the specific active ingredients and the source and magnitude of exposure.

Use of retrospectively recalled symptoms as a marker of exposure is notoriously inaccurate, since symptoms (such as headache or "head tension", sleep disturbances, feeling nauseated or "dizzy", chest pain and difficulty in breathing, feeling weak, tremor or "shaking", numbness, "burning" or "tingling" sensations, problems with vision, easy fatigability and cognitive symptoms, including confusion and difficulty in concentrating) are non-specific and subject to recall bias. Furthermore, these symptoms are indicators of acute or subacute effects, not necessarily present in chronic or prolonged exposures. Therefore, quantitative estimation of the exact level of pesticide exposure is extremely complex. Thus, in most studies the level of occupational exposure to pesticides is crudely divided to low, moderate or high. Moreover, it is extremely difficult to assess pesticide exposure not related to occupation. Finally, it is debatable whether we should measure peak, average or cumulative exposure to pesticides as an index of the exposure for an individual. Various possible biological and epidemiological markers of chronic exposure to pesticides are currently under intense investigation, given the important health implications of this exposure.

Despite the limitations presented above, there is an increasing number of studies linking exposure to pesticides to cognitive dysfunction and even overt dementia, including AD dementia (Table 1). These studies are presented below, taking into account the fact that dementia, especially AD dementia, is part of a continuum, spanning from mild cognitive and neurobehavioral deficits to mild cognitive impairment and then to overt dementia. In addition, the reader should bear in mind that the boundaries among these three entities are at times arbitrary and hard to accurately define.

2.2. Pesticides and their possible cognitive and neurobehavioral effects

There have been several studies linking pesticide exposure to cognitive and neurobehavioral deficits (Colosio et al., 2003, 2009; London et al., 2012). In these studies, subjects exposed or supposedly exposed to pesticides or related compounds (e.g. industrial compounds or chemical warfare reagents) underwent a series of neuropsychological tests to assess their cognitive and neurobehavioral skills. In some of these studies, researchers were privileged to be able to compare pre- and post- exposure levels of performance. In case this was not feasible, the comparison was with a carefully selected control group.

In the PHYTONER study performed in Bordeaux, France, Baldi et al. (2011) recruited 929 vineyard workers, with a mean age of about 50 years and at least 20 years of agricultural work. The study population was further divided into separate categories of exposure (none, direct and indirect). Reexamination of 614 individuals after four years, using a questionnaire and nine neurobehavioral tests, showed cognitive decline associated with chronic pesticide exposure. Specifically, exposed individuals had a mean two-point MMSE (Mini-Mental State Examination) score decline and faster decrease in performance over time compared to non-exposed subjects. More extensive evaluation showed that impairment in visual working memory (according to the Benton Visual Retention Test) and other cognitive domains was more prominent in individuals exposed to pesticides. In this study, the association between exposure and mental decline was surprisingly most pronounced in women and in subjects with high levels of education and no alcohol consumption. This could be interpreted that either the absence of factors negatively affecting cognitive function (low education level, high alcohol consumption) allows the effect of pesticide exposure to be detectable or, alternatively, the presence of these factors accentuates the effect of pesticide exposure. Unfortunately, in accordance with other studies, most participants could not recall the exact type of pesticide they were exposed to and thus a direct association between specific chemical agents or even combinations of pesticides (Hernández et al., in press) and cognitive impairment could not be established.