Assessment of Pesticide Biohazards in Neurodegenerative Diseases; Data Analysis Statistical Study

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Abstract

Background: The initiation of late onset neurodegenerative diseases remains unknown. New researches suggested that prolonged exposure to pesticides might lead to the initiation of neurodegenerative diseases, but the results were subject to controversy. **Aims:** The present study aimed to demonstrate an update data-mining to compare published data for studies comparing role of pesticide in induction of neurodegenerative diseases (Parkinson's diseases, Alzheimer's diseases, and Amyotrophic lateral sclerosis) Results: A clear association has been noticed across different studies regarding correlation between pesticide exposure and Parkinson's disease or Amyotrophic Lateral Sclerosis (Odd Ratio >1), nevertheless, the association was weaker between exposure to pesticide and the development of Alzheimer's disease (Odd Ratio close to 1) Conclusions: There is good quality evidence that the impact of pesticide in initiation of neurodegenerative disease is statistically approved. However, there is inconclusive evidence from randomised controlled trials to show significant induction of neurodegeneration. More research is needed particularly long-term controlled studies on laboratory animals.

Keywords: *agriculture, pesticide, neurodegenerative, Alzheimer, Parkinson, epidemiology.*

Introduction

Aging-related diseases are worldwide major health issue, Alzheimer's disease (AD) distributionconstitute two-third form of dementia and is described as a continuous diminishing of memory and other intellectual capacity[1]. Alzheimer's disease (AD),Amyotrophic Lateral Sclerosis (ALS), and Parkinson's disease (PD) are described as major motor health problems and it has been demonstrated that there is a correlation between these neurodegenerative diseases and the pesticide exposure[2]. The organophosphate (OP) insecticides are discovered very early last century, however, started to find application worldwide due to their effectiveness as an insecticide with low human toxicity[3].

OP can be easily absorbed through GIT, respiratory system, mucous membrane, and skin[4]. OP toxicity is apparently common in farmers resulting in great morbidity and mortality, particularly in developing countries with rigorous agriculture[5]. However, the available data provide no clear-cut idea about the prevalence of the disease and the reported acute toxicity cases are relatively high (approximately 3000000 cases worldwide plus 220000 death rates)[6]. Nevertheless, in absence of accurate statistical study, these records provide only limited information about the real estimate due to unavailability of medical records in all countries and/or undiagnosed cases[7].

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Inhibition of the enzyme acetylcholinesterase is the principle mode of action of the OP insecticide, reducing the availability of the neurotransmitters acetylcholine (Ach) at synaptic clefts resulting in peripheral and central stimulation of nerve and muscle[8]. Toxicity with OP is associated with autonomic overstimulation, movement impairments, muscular rigidity, reduction of motor activity and respiratory failure[9]. Recovery is usual and it takes 1-2 days until all the symptom disappear, however, delayed effects are uncertain and continuous exposure results in worsening of the condition overtime leading to neurological impairment, such as, mild paralysis, sensorineural polyneuropathy, cognitive dysfunction and psychiatric disturbances. This systematic review provides statistical clue about possible correlation between pesticide exposure and the potential development of long-term morbidity[10].

Study design and methods

We searched Iraqi Virtual Science Library (IVSL),PubMed, Cochrane Library MEDLINE, EMBASE, and the Chinese Biomedical Database (CBM), for the 2 target words *'pesticide, neurodegeneration'* and target English papers. To be included, papers should be original work and full text articles. All published manuscripts were screened by reading the title and abstract for potential relevance to this research topic; whenever the title and abstract did not obviously state the degree of relevance, the manuscript itself was reviewed. To overcome search bias, another researcher conducted the review procedure independently; only studies jointly accepted by the two independent reviewers were taken into considerations. To simplify tracking the results in the present study, the results were categorised into Alzhiemer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis.

The online literature investigation revealed 827 publications, of which 731 duplicate studies were identified and thereby excluded, unrelated or not epidemiological study. The 96 target articles were downloaded and investigated carefully by two independent colleagues. We further removed another 14 unrelated publication from the total (Mixing other disease with other neurodegenerative disease). Ultimately, 82 trials were comparable to our inclusion standards, and the summarised data listed in figure 1, 2, and 3; related to Alzheimer's, Parkinson's and Amyotrophic Lateral Sclerosis, respectively. Only 82 epidemiological studies trials included patients diagnosed with neurodegeneration by specific criterion.

Results and Discussion

The collected epidemiological studies confirm that there is a great association between pesticide exposure and the development of neurodegeneration, more than 90% of these collected studies were showed that the odd ratio (OR>1) indication that there is a risk of developing the neurodegeneration due to exposure to these organic substances for long-periods (see figure 1, 2, and 3). The detailed information about the year, author, type of studies, and sample size about the collected epidemiological studies were mentioned below in Figure 1, 2, and 3.

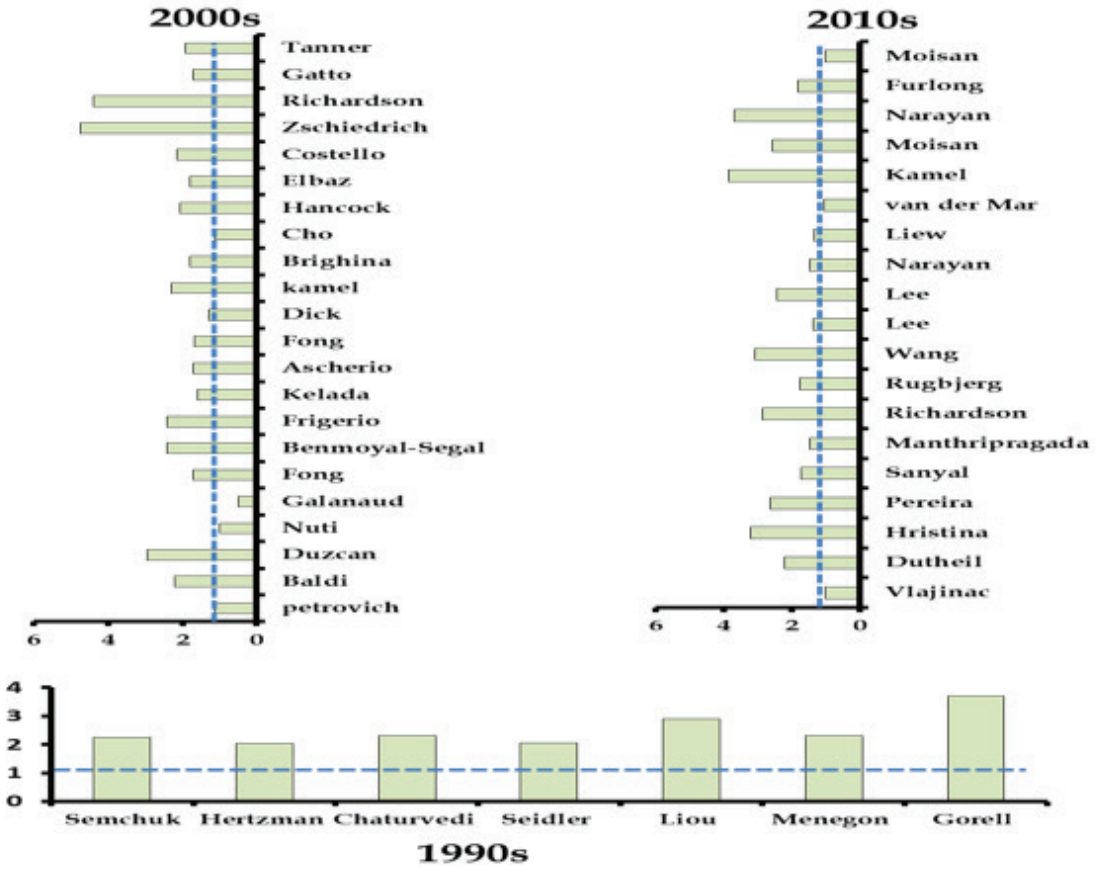

Figure 1. Odd ratio of different epidemiological study of pesticide exposure and development of Parkinson's disease.[(2000s Petrovich[11], Baldi[12], Duzcan[13], Nuti[14], Galanaud[15], Fong[16], Benmoyal-Segal[8], Frigerio[17], Fong[16], Dick[18], Kamel[19], Brighina[20], Cho[21], Hancock[22], Elbaz[23], Costello[24], Zsciedrich[25], Gatto[26], Tanner[27]), (2010s Vlajinac[10], Dutheil[28], Hristina[10], Pereira[29], Sanyal[30], Manthripragada[3], Richardson[31], Rugbjerg[32], Wang[6], Lee[33], Narayan[4], Liew[34], van der Mar[35], Kamel[19], Moisan[36]), (1990s Semchuk[37], Hertzman[38], Chaturvedil[39], Seidler[40], liou[41], Menegon[42], Gorell[43])]

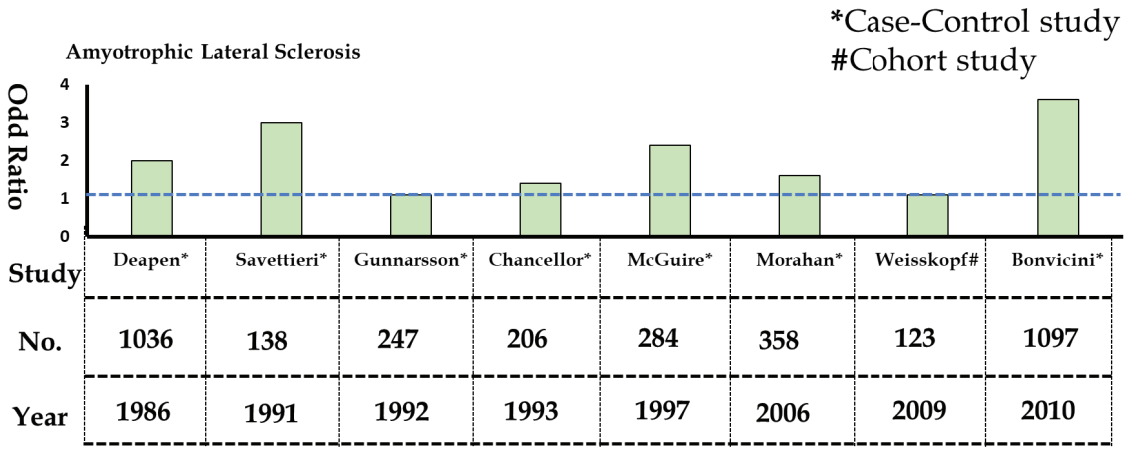

Figure 2. Odd ratio of different epidemiological study of pesticide exposure and development of Amyotrophic Lateral Sclerosis. [Deapen[44], Savettieri[45], Gunnarsson, McGuire[46], Morahan[47], Weisskopf[7], Bonvicini[48]]

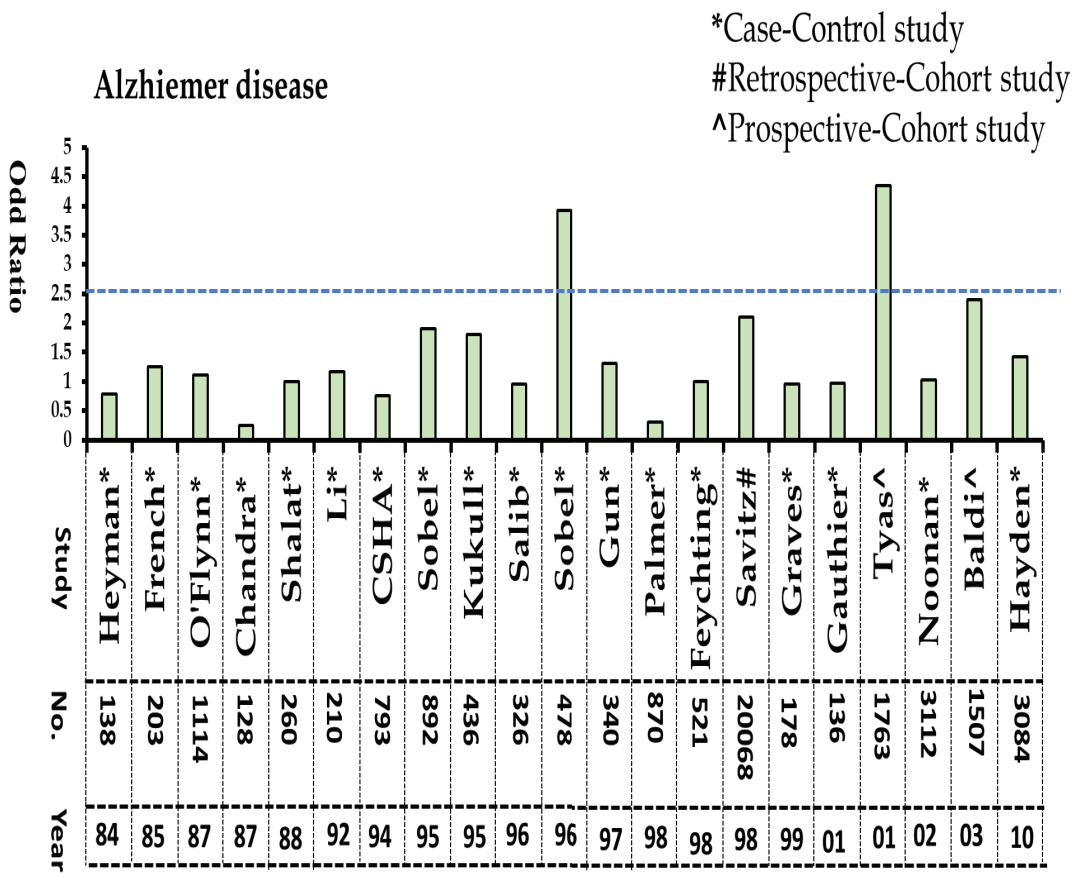

Figure 3. Odd ratio of different epidemiological study of pesticide exposure and development of Alzheimer's disease. (Hyeman[49], French[50], O'Flynn[51], Chandra[30], Shalat[52], Li[5], CSHA[53], Sobel[54], Kukull[55], Salib[56], Sobel[54], Gun[57], Palmer[58], Feychting[59], Savitz[60], Graves[61], Gauthier[62], Tyas[63], Noonan[1], Baldi[64], Hayden[65])

The causative agents involved in initiation and progression ofneurodegenaerative diseases is yet unknown. A great efforts has been paid by scientists in an attempt to identify the causative agent involved in these diseases. The impact of these disease imposed a great burden on the individual and society due to high rate of morbidity and mortality. The health system funding of the neurodegenerative diseases is relatively high per annum as compared to other diseases including cardiovascular ones. Most of these neurodegenerative diseases start at elderly age group (>60 years). Identifying the causative agents is of great importance in determination of the underlying pathology of the disease to reduce its prevalence; reducing the burden on health care provider and reduce health cost budgets of geriatric-living cost. In the present statistical study we tried to identify the link between pesticide exposure and neurodegeneration in elderly age group through reviewing other case control studies conducted at different timeline and different area in the world. Many variables has been identified in the present study which could be a limitation of our study, including types of pesticides used which are in most cases unidentified by the participant or they reported their exposure to different agents during their life-time. The age of the participant varies (65-90 years) and this needs to be counted as an important variables because the neurodegenerative disease by default is age linked. The duration of our study is extended over 4 decades (1980s-2010s) which is regarded as an additional variables to be considered because during this extended period of time; different new pesticides were potentially introduced in farming. Therefore, the outcome of our

study is questionable and should be explained in the shadow of these variables. The outcome confirm that exposure to pesticide in field area for pesticide-dealers has been clearly associated risk of developing NDD with approximately overall studies showing an odd ratio of greater than 1.

The highlighted studies collected presently confirm that age is important factor in these diseases. There are a clear link between the exposure to pesticide and increased risk of development of neurodegenerative disease and this association is reciprocal to increased age, however, there is no consent on the age or age range at which pesticide could induce or increase the risk of association. Clear association with age were noticed at elderly (after 70)for both PD and AD, however, ALS shown onset at different age ranges excluding the possibility of association between pesticide exposure and age of participant. However, no differences were reported to exist in relation to sex variation. The studies records shown equal involvement of male/female in the study with no reported variation between studied group. The timeline of exposure to the pesticide showed important consideration regarding earlier type of pesticide which were reported to be more neurotoxic than those newer agents. In 1990s the available agents has been shown to be more neurotoxic than those newer agents introduced in 2010s.

The present study aimed at identifying the correlation between the exposure to pesticide and theincident of neurodegenerative ailments[11]. However, so far there is no idealagreement about the link between exposure to pesticide and neurodegeneration initiation, therefore, more investigation and data analysis is needed before a clear–cut conclusion is drawn[36]. Age is a principle factor for neurodegeneration exaggerated by pesticide exposure. Four mechanisms exist for illustration of the pesticide-induced neurodegeneration linked with aging, these include; oxidative mechanism of action, reaction between amyloid and organophosphates, cognitive impairment, and neuronal or haemostatic damage[14].

The relationship between the rate of exposure to pesticide and the incident of Parkinson's, Alzheimer's disease, and Amyotrophic lateral sclerosis is theoretically acceptable due to structural similarities between neurotoxin 1-methyl-4-phenylpyridinium (MPP+), a metabolite of 1-methyl,-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); with some pesticides, insecticides, and herbicides[30]. Researchers has recently found a link between the molecular mechanism of action of the agricultural compounds and the development of different disease[37]. For instance, rotenone an enzymatic process in mitochondrial membrane complexes enzyme (Complex I) which are involved in oxidative phosphorylation reaction resulting in mitochondrial depolarisation leading to cellular necrosis[32]. Simple defect in this Complex I-enzyme could results in pathophysiological features of neurodegenerative disease. Investigators have found that organochlorines generate reactive oxygen species, accumulation of a-synucleinbiomolecules, impairment of the ubiquitin-proteasome system and the disruption of mitochondrial membrane potential, and stimulation of dopamine production leading to intracellular dopamine vesicle exhaustion[66]. Moreover, paraquat long-term dopamine overproduction and consequently reduction in dopamine synthesis due to activation of N-methyl-D-aspartate (NMDA) receptor and suppression of the complex I of the mitochondrial membrane potential transport chain resulting in cellular apoptosis or necrosis[35]. Carbamate inhibits ubiquitin proteasome system (UPS) by preferential damage to TH+ neurons and elevated alpha-synuclein levels. Imidazoles (e.g. benomyl), dithiocarbamates (e.g. maneb, and ziram), organochlorine, and other pesticides can inhibit aldehyde dehydrogenase (ALDH) enzyme[66]. Recent studies indicated the importance of ALDH in involvement in the pathology of neurodegenerative disease [16].

Conclusion

To sum up; oxidative stress and neuronal inflammation, microtubule modification together with compromised axonal transport, beta amyloid formation, calcium homeostasis and mitochondrial dysfunction are

all factors that at least are able to impact onintellectual or motor decline. The major challenge for future investigators is in demonstration of variables which required to be controlled in epidemiological studies and designing more focused and translational experimental studies.

Conflict of Interest: Nil

Source of Funding: Self

Ethical Clearance: Taken from College of Pharmacy Research Ethics Committee

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