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Environmental genesis of Alzheimer's disease: A proposed role of air pollution and insecticides in AD pathogenesis

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cerebral deposition of extracellular amyloid plaques and intracellular neurofibrillary tangles. However, these neuropathological changes are final symptoms and the earliest manifestation of pathological changes is an increase in the level of cellular oxidation caused by free radicals. As our environment is abundant in factors promoting this process, the paper presents the facts concerning the relations between air (i.e. smog and pesticides) and soil pollution (i.e. pesticides) and AD prevalence.

Keywords, Alzheimer disease, air pollutants, pesticides, insecticides, herbicides

Alzheimer's disease (AD) is characterised by presence of amyloid plaques and neurofibrillary tangles, accompanied by grave neuronal loss in the brain. The major components of amyloid plaques (Aβ42) are small fragments of peptides (of 42 amino acids), deriving from the amyloid precursor protein (APP), which is a type of integral membrane protein. Aβ is generated from APP as a result of proteolytic activity of enzymes, α, β, and γ secretases. Normally APP is cleaved by α secretase, followed by γ secretase, which leads to production of a soluble form of APP. However, an insoluble 42-AM form of APP release may also take place, as a result of action of β and γ secretase. The products of this cleavage path accumulate extracellularly as large, insoluble amyloid fibrils that elicit both cytotoxic and inflammatory responses [1].

Neurofibrillary tangles are described as built up of paired helical filaments (PHF), which are derivates or transformation products of filaments.

Filaments are composed of neuronal tau protein, which in physiological processes performs structural and transport tasks in axons. As long as tau protein is hypophosphorylated, it shows high affinity to microtubules, while hyperphosphorylated tau protein is subject to polymerisation, becomes insoluble and is redistributed into PHF [2]. This underlies the destabilisation of microtubules and causes a decline in their transport function [2]. Moreover, it was demonstrated that PHF induce secondary generation of free radicals [3].

Although even nowadays, in the latest publications concerning AD [4], a statement that an increase in β-amyloid levels is a key factor in pathology of the disease can be found, it was well pointed out by Nunomura et al. [5] that neuropathological changes in people suffering from dementia are final symptoms by definition (of neuropathology). The most frequent earliest manifestation of pathological changes is an increase in the level of cellular oxidation in vulnerable neurons (i.a. the neurons in which a typical pattern of neuronal damages caused by AD develops later) [for details see 6].

The defects caused by free radicals appear mainly in the regions of the brain which have the highest metabolic rate and show the highest level of mitochondrial expression.

Knowing that the presence of both tangles and amyloid plaques is linked to inflammation [7] as well as peroxidation caused by free radicals [8] and that our environment is abundant in factors promoting those processes, an analysis of air and soil pollution in relation to AD prevalence was performed.

AD AND EXPOSITION TO AIR POLLUTANTS

Air contamination may stem from the presence of gases (i.a. ozone), air-borne dust, metals or endotoxins. It may lead to chronic respiratory tract inflammation, an increase in neuronal expression of nuclear factor, induction of nitric oxide synthase, damages in nasal mucosal barrier and blood-brain barrier and cerebral mioangiopathy. All those defects trigger inflammatory mediators secretion, in consequence of which neurodegenerative processes ensue.

In people of severely polluted regions (Mexico City, Monterrey) an increased level of COX-2 (cyclooxygenase-2, an inflammatory mediator) and traces of oxidative DNA damage in the hippocampus and olfactory bulb were found – which means that typical for AD early changes occurred. A control group comprised people from 5 small towns, in whom no such changes were observed. Although this research did not show any elevation in the number of neurofibrillary tangles or β-amyloid plaques, these symptoms are linked to later AD pathology

manifestation and both people from the city and towns were relatively young (no older than 60), which means that in their brains mostly a soluble form of β-amyloid accumulated [9]. Similar results were obtained in a study on influence of polluted environment on the olfactory system and the brain in dogs in Mexico City and Tlaxcala [10]. The dogs were examined since their 7th day up to 10th year of life. As a result it was demonstrated that the duration of exposition affected the severity of histological and biochemical symptoms, which were similar to those observed in people suffering from AD. The study covered analysis of changes in the brain cortex, hippocampus, olfactory tract and olfactory bulb. It was established that the dogs from polluted environments showed injuries in the respiratory and olfactory ducts, DNA damage, increase in neuronal expression of nuclear factor, elevated level of COX-2, induction of nitric oxide synthase, raised level of metallothioneins, ApoE, APP and β-42 amyloid itself. The most striking changes were observed in the olfactory bulb and hippocampus[11]. The research also confirmed the notion that the observed increase in soluble form of β-42 amyloid level, yet with no senile plaques in people could result from their young age, for presence of aggregated forms of β-amyloid was observed only in dogs older than one year. This, however, does not mean that only elderly people are vulnerable to pollution in the environment, since the subsequent studies (also carried out in Mexico City) covered a group of much younger individuals, including children, adolescents and young adults, in which it was demonstrated that neurodegenerative processes may begin in childhood and adolescent years [12, 13]. Further investigation is due on whether moving from the polluted areas may lower the risk of the disease onset and if so, to what extent the changes are reversible.

Nevertheless, as neuroinflammation is a critical component of the brain's responses to air pollution, it seems that nonsteroidal anti-inflammatory drugs may offer neuroprotection. Oral administration of Nimesulide® showed neuroprotective effects in dogs exposed to air pollution [14].

PESTICIDES

On the contrary to the results of research on the effect of air pollution on the AD prevalence in inhabitants of small towns, living in rural area seemed to be associated with a bigger threat of this disease [15]. The cause for this may lay in the use of pesticides, therefore the correlation between exposition to them and AD prevalence has recently become an object of interest of researchers. There are only few studies on correlation between AD prevalence and exposition to

pesticides and their results are sometimes contradictory [16, 17]. As it was noted by the independent and prestigious National Academy of Sciences Institute of Medicine (IOM) „'*inadequate/insufficient' evidence of an association between this disease and insecticide exposure*"… stems from… „*difficulty in studying the relationship between environmental exposures and neurological disease due to uncertainty in diagnoses, long latencies associated with this illness and problems with self-reported exposure data*",… for… „*the subjects often have difficulty recollecting which specific pesticides they may have been exposed to*" [18]. Unfortunately, these are not only reasons for discrepancy between the results. They may also arise from the fact that the mechanisms of particular chemicals action are completely different and in many papers a whole group of pesticides was taken into consideration, failing to divide them into data concerning herbicides and insecticides. Even within those two large groups the differences in likelihood of initiating changes triggering processes leading to AD development are tremendous.

The threats posed by pyrethroids, which open sodium channels, and by the insecticides which inhibit cholinesterase, i.e. carbamate and organophosphate insecticides [19] are completely different. The threat by insecticides, which affect nicotinic receptors (i.a. nicotine and neonicotinoids), or inhibit cholinesterase, is highest, as these substances affect directly cholinergic transmission, which remains pivotal for memory processes. Additionally there are studies showing changes in the levels of neurotrophins nerve growth factor and brain-derived neurotrophic factor in the cortex and the hippocampus [20] and especially temporary memory disorders after exposition to the latter group of insecticides [21] may provide a supportive evidence for relationship between exposure to insecticides and AD. This interpretation finds support also in the studies showing that the risk of AD is higher in people who were exposed to organophosphates than in those exposed to organochlorine compounds [22, 23]. However, organochlorine insecticides have also been demonstrated to be neurotoxic and cause oxidative stress, therefore, they may also contribute to the AD threat. This is presumably the reason why in 100% of people suffering from AD - p,p'DDE was found in serum, while it was found only in 86% of individuals in the control group [23]. Moreover, some fungicides (like maneb) and insecticides (like retenone) may cause damages to nerve functioning by inhibititing mitochondrial functions, which in turn cause an increase in free radicals production [for details see 6]. This increase in most cases is an opening phenomenon to the subsequent changes occurring during AD onset.

An analogous situation occurs with herbicides. Some of them uncouple oxidative phosphorylation (dinitrophenols) and some increase production of free

radicals (paraquat-like herbicides) [19]. Thus, those two types of herbicides have similar effect on the organism and moreover, their action may contribute to AD development, contrary to the herbicides which show a mode of action similar to that of gibberellins. However, one must not fail to consider some additional compounds, not always taken into account in toxicity threat assessment. Their role in creating the risk of AD development may be no lesser than this of the active substance. For instance, it is hardly possible to ignore the potential influence of additional ingredients able to inhibit cytochrome P450.

However, even such imperfect analyses shed some light on the prospective threats and so for example, French studies on nearly 3000 people showed that occupational exposure to pesticides raises the risk of AD onset 2.39-fold [21]. The studies were performed on people dealing with crop spraying, viniculturists and people from rural areas. Also some newer research, performed near Bordeaux on 929 vineyard workers, suggested long-term cognitive effects of chronic exposure to pesticides and raised the issue of the risk of dementia [24] .The results clearly indicated that although living in such areas (of low pollution) diminishes the risk of the disease development, it is nevertheless raised by the contact with crop protection chemicals.

Unfortunately, it was not pointed out which of the 23 chemicals taken into consideration proved themselves to be the most dangerous. However, such assessment can be found in a different work, by Tyas et al. [25], where in the group of workers exposed to fumigants and defoliants a 4.35-fold increase in the AD development risk was observed. An elevated risk of AD onset in relation to occupational exposure to pesticides was also showed by Santibanez et al. [26], who analysed 24 epidemiological studies published up to 2003 via Pub Med and Toxline. Less spectacular were the results of another paper [27], which analysed the pathogenetic effect of herbicides and insecticides in Saguenay-Lac Saint-Jean region of Canada, showing only a poor impact of insecticides alone. However, since it was demonstrated that chlorthiamid causes injuries in the olfactory epithelium [28] – and repetitious exposure leads to permanent damages in the epithelium and afterwards in the bulb, one may expect this herbicide to play a key role in the AD initiation processes, too (for it was proved that the olfactory bulb damage triggers degenerative changes in the hippocampus) [for details see 6] – but assessing the risk of AD initiation was not the objective of this research.

Another indirect evidence for the relation between the prolonged contact with pesticides and the risk of AD is given by the research on the effect of exposure to malathion [30]. The data reveal that it increases the risk of depression, which in turn is sometimes indicated as one of the risk factors for AD (by elevating the risk 2-fold, and even considered as a prodromal hallmark of AD [for details

see 6]). It is also a well-known fact that people engaged in crop protection tend to suffer from temporary memory deficits [15]. It is even more alarming that such short-term memory deficits were also observed in children exposed to organophosphate pesticides both prenatally and during childhood [29].

THOROUGH RECOGNITION OF THE THREAT = MORE OPPORTUNITIES FOR ITS PREVENTION

The studies on the impact of pesticides on the risk of AD development are, 1/ extremely laborious (lack of co-operation from the subjects), 2/ longstanding (over 5 years), 3/ expensive (brain CT), 4/ the risk depends on the age at exposure (the earlier exposition, the larger risk [14]), 5/ need to consider numerous side-factors, as it was demonstrated above (the results may be affected by general environment pollution). Such analyses are nevertheless crucial. Abandoning all forms of chemical pest control is, by all means, out of question on the current stage of our knowledge on the alternative means of crop protection. Yet, it should be taken into thorough consideration whether the people exposed to pesticides should not be subject to preventive supplementation with non-steroid anti-inflammatory drugs and/or with free-radical controllers (such as vitamin C, E or melatonin). Moreover, some results clearly suggest a chance for the disease prevention, since it was proved that administrating zinc reduced the neurotoxic effect of malathion [30], it has been also demonstrated that oestrogen therapy may contribute to prevention, attenuation and even delay the onset of AD [31]. Even more spectacular beneficial effect was observed in people drinking 2-4 cups of coffee a day, in whom the reduction of the risk of AD was as high as by 30% [32]. Unfortunately, these data come from a research on the AD prevalence only and do not consider exposition to pesticides. Nevertheless, given that caffeine is an antagonist of adenosine receptor, which in turn has been implicated to take part in memory and cognitive performance, and that caffeine can reduce the negative effects of β-amyloid, it is unquestionably worth further research, especially in terms of its interaction with insecticides. And more thorough recognition of the threat can offer better opportunities for its prevention.

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