G Ital Med Lav Erg 2018; 40:3, 162-166
ISSN 1592-7830

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Occupational exposures, biomarkers and neurodegenerative diseases

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ABSTRACT. Brain aging is marked by progressive changes and characterized at cellular, and organ dysfunction occurring in several areas of the brain. The main processes have all in common the deposition of proteins that the brain cannot metabolize anymore. While the aging processes is generalized and present in all individuals is characterized by great variability among individuals with a minority of subjects that are very healthy even in very old age.
Epidemiological and laboratory studies suggest that environmental and occupation exposures years or decades before a diagnosis can trigger the processes that ultimately result in a neurodegenerative disease. The major areas of research in occupational epidemiology will be revised with the role of heavy metals, organic solvents, and pesticides as the main focus of this report.
The public health especially in the field of occupational epidemiology of NDG diseases needs an integrated approach. This has been recently named "convergence science", a transdisciplinary approach for a research which frames in the same convergence view several fields from epidemiology to physics, informatics, ecology to solve complex questions, including the role of occupation, in biomedicine.

Key words: *neurodegenenerative diseases, toxicants, solvents, metals, public health.*

RIASSUNTO. Esposizioni professionali, biomarkers e malattie neurodegenerative. L'invecchiamento cerebrale è segnato da cambiamenti progressivi caratterizzati da disfunzioni di cellule e d'organo in diverse aree del cervello. I principali processi sono accomunati dalla deposizione di specifiche proteine che il cervello non è più in grado di metabolizzare. Mentre il processo di invecchiamento è generalizzato e presente in tutti gli individui, è caratterizzato da grande variabilità tra individui, con una minoranza di soggetti che sono in piena salute in un'età avanzata.
Studi epidemiologici e di laboratorio suggeriscono che esposizioni ambientali e occupazionali anni o decenni prima la diagnosi possono innescare il processo di degenerazione che culmina in una malattia neurodegenerativa. Le aree di maggiore ricerca della epidemiologia occupazionale saranno rivisitate con un particolar focus sul ruolo di metalli pesanti, solventi organici e pesticidi.
La salute pubblica necessita, in particolare nel campo della epidemiologia occupazionale delle malattie neurodegenerative, un approccio integrato. Questo è stato recentemente definito "scienza della convergenza", un approccio interdisciplinare per una ricerca che inquadri insieme epidemiologia, fisica, informatica, per dare risposte appropriate alle complesse domande della biomedicina.

Parole chiave: malattie neurodegenerative, sostanze tossiche, solventi, metalli, salute pubblica.

Brain aging is marked by progressive changes and characterized at cellular, tissue and organ dysfunction occurring in several areas of the brain. The main processes have all in common the deposition of proteins that the brain cannot metabolize anymore. While the process is generalized and present in all individuals is characterized by great variability among individuals with a minority of subjects that are very healthy even in very old age. The clinical manifestations are broad involving several domains mainly affecting the cognitive performances but also motor features and functional features of the whole body. These changes are part of the aging pathological and physiological processes. At the same time these changes are also risk factors for a spectrum of central nervous system neurodegenerative disorders including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS).

Neurodegenerative disorders are in most cases thought to have complex etiologies. In each disorder, degeneration affects selected neuronal populations, resulting in characteristic clinical syndromes.

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).

Globally, neurological disorders have a important impact both on mortality and disability: they account for about 5% of all deaths and disability-adjusted life-years from non-communicable disease. All these diseases are without an effective cure. Neurodegenerative and neurological diseases in general are probably without precise strategies for identification and research or at least in an early phase compared to other groups of chronic diseases as cancer, cardiovascular, and diabetes (2,3).

Neurodegenerative disorders are heterogeneous, complex and most cases are not typical but transitional phenotype involving many domains. There are no effective therapies even if for the first time many new therapies addressing causal pathways are on the way (4).

The focus to lower the load should be therefore on the identification of modifiable risk factors and prevention.

The causation of neurodegenerative diseases as in many chronic diseases is linked to a variable mix genetic, environmental and life style risk factors.

Acquired risk factors determined by the environment are determined outside human choice (passive) or due to specific behavior and active actions.

Some of these active behaviors are linked to work and exposures specifically linked to work in young and middle age are possible risk factors for aging related CNS diseases.

Epidemiological and laboratory studies suggest that environmental and occupation exposures years or decades before diagnosis can trigger the processes that ultimately result in a neurodegenerative disease. Most cases are now thought to arise from a combination of genetic risk factors and environmental influences.

Identifying specific chemicals is important to understanding disease pathogenesis, yet few studies investigated specific compounds. The quantification through biomarkers of occupational exposures is one of the challenges (Figure 1).

The effect of environmental contaminants on health is a major concern because over the last decades, several studies worldwide have shown how chemicals present in our environment can profoundly affect the aetiology of chronic diseases. Indeed, pesticides toxicity has been clearly demonstrated to alter neurological functions and numerous epidemiological studies have shown a relationship between pesticides exposure and the aetiology of neurodegenerative disease. The term pesticide includes herbicides, insecticides, fungicides, and rodenticides, and represents hundreds of chemicals with widely different structures and biologic effects.

Epidemiological results were found in some cases contradictory because there is considerable heterogeneity in results likely due to methodological differences, study design, control selection, differences in exposure assessment methods and diagnosis of patients. In this heterogeneous amount of studies pesticides are linked to occupational work in agriculture and have been constantly linked to Parkinson's disease and amyotrophic lateral sclerosis but recently also to Alzheimer's disease (AD).

Occupational exposure to pesticides compared with unexposed was associated with a relative risk of 2.29 (95% confidence interval [CI] 5 1.02–5.630) of developing AD in a cohort study of 1500 elderly participants (5). In another study of more than 17,000 patients living in southern Spain, the prevalence of AD was twice as high in those living in areas with high pesticide exposure compared with areas of low exposure (6).

Several studies have investigated associations of pesticide exposure and Amyotrophic lateral sclerosis (ALS) risk (7-9). Although not all were 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 (10,11).

The research has also focused on associations between neurodegenerative disease and occupational exposure to organic solvents. Common solvent-containing products available for both industrial and residential use include adhesives and fixatives, paints, lacquers, degreasers, pharmaceuticals and agricultural products. Most routine exposures occur in occupational settings, with activities such as painting, construction, and furniture finishing; metal degreasing and finishing; mechanical and refrigeration sys-

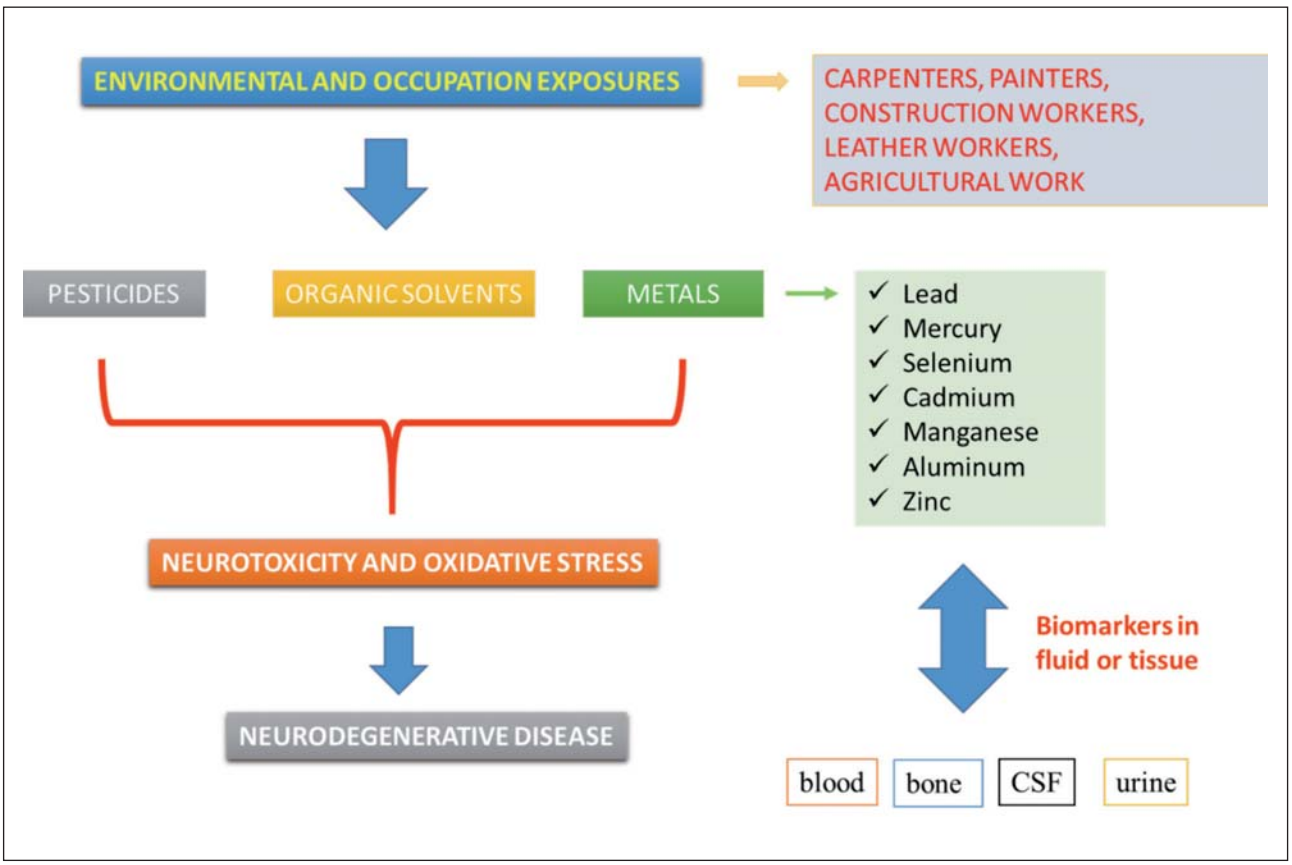

Figure 1. *Biomarkers role in occupational epidemiology*

tems maintenance; rubber, plastic, textile and leather production; and dry cleaning. Solvent exposures from these activities occur primarily through two routes, inhalation and cutaneous contact, both of which can be significant. Ingestion also occurs, typically from unintentional or accidental exposures. Neurotoxicity derived from exposure to these substances requires weeks to years and, in some cases, decades to produce cell dysfunction and cell death that result in detectable neurological alterations. The special sensitivity of the nervous system to toxicant exposures and shared mechanisms by which toxicants may act to disrupt neurological function are investigated. However, data interpretation is often difficult due to exposure to mixtures and variability of exposure levels between individuals.

Occupational exposure to organic solvents was found associated with an increased risk of Parkinson's Disease (PD) and in particular, researchers found a six-fold increase in the risk of developing Parkinson's in individuals exposed in the workplace to trichloroethylene (TCE). The risk of developing the disease increased significantly with the addition of two other solvents, perchloroethylene (PERC) and carbon tetrachloride (CCl4). No statistical link was found with the other solvents examined in the study (toluene, xylene and hexane) (12,13).

Exposure to 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) (14). However, occupational exposure to solvents was not associated with AD in a meta-analysis analyzing case-control studies (15).

Some studies over several decades have assessed the association of solvents and ALS, with many finding an increased risk associated with self-reported solvent exposures (16-18) and/or occupations with likely exposure, such as carpenters, painters, construction workers, or leather workers (18-20). As with pesticides, however, most studies evaluated solvents as a general class, rather than specific agents.

One difficulty is that several of these neurodegenerative conditions (for example, Parkinson's disease) are not single disease entities but a heterogeneous group of clinically similar conditions. It may be that some individuals have solvent induced neurodegeneration but these are lost among the majority of sufferers whose condition is not due to solvents.

Ambient total suspended particles from traffic have been associated with an increased risk of PD (21). 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 pollution areas (22). Pollution-induced inflammatory brain mechanisms were found also, suggesting that air pollution may be involved in the development of PD and/or dementia.

The role of metals in neurodegenerative disorders has been also considered. Overexposure to any of several metal ions, including lead, mercury, selenium, cadmium, manganese, arsenic, copper, aluminum, and zinc, is known to be neurotoxic.

Some investigators have demonstrated higher levels of metals ions in the blood, bone, cerebrospinal fluid, urine of patients with ALS compared to controls (23), and aluminum was found in high concentrations in brain regions with many neurofibrillary tangles from AD patients (24,25).

Heavy metals have both acute and chronic effects. The chronic effects could be determined by low concentration in the soil, where the contamination last for many decades.

Many metals, like lead and manganese have been used for centuries while others compounds like polychlorinated biphenyl (PCB) is an organic chlorine compound, are relatively new in the industrial processing.

The entry routes in the human body are several: skin, lungs, gastro-intestinal system. The routes of elimination are several as well: skin, lungs, colon, and kidneys. The different compounds are prone to accumulate in different tissues if the elimination system does not properly work or the dose is too high. The excess that is not metabolized tend to accumulate in several tissues like fat, bone marrow, muscle, blood, liver. One of the main organ of deposit is the brain and the whole central nervous system.

In a whole field approach, using mortality data from 22 states in US for the years 1992-1998. Several specific occupations including pesticides, solvents, magnetic fields, and welding fumes were evaluated (20) the occupations hypothesized with these approach presented significant elevated mortality odds ratios (MOR) for the neurodegenerative diseases. Occupations with the largest MORs were (a) for young onset dementia dentists, graders/sorters (non-agricultural), and clergy; for Alzheimer's disease were bank tellers, clergy, aircraft mechanics, and hairdressers; for Parkinson's disease (PD) were biological scientists, clergy, religious workers, and post-secondary teachers; and) for motor neuron disease (MND)-veterinarians, hairdressers, and graders and sorters (non-agricultural). Teachers had significantly elevated MORs for all four diseases, and hairdressers were elevated for three of the four. Neurodegenerative disease risk was associated with many occupations, 60 Hz magnetic fields and welding. In a similar study conducted on death certificates in 27 states, several occupations were found associated with neurodegenerative disorders such as teachers, medical personnel and machine operators were identified. Clusters of three NDG diseases were identified in occupation involving electromagnetic fields, solvents and pesticides (26).

Similarly, a role of occupation was detected in a case control study conducted in the US Individual electrical occupations were associated more strongly with disease than overall electrical occupations. The risk was particularly high for amyotrophic lateral sclerosis, for which relative risks ranged from 2 to 5 across several job categories. The largest associations with all three diseases occurred for power plant operators (27).

The importance of magnetic field was indeed described as non relevant in a mortality study in the UK. In the period 1973-2010, the mortality was estimated a co-

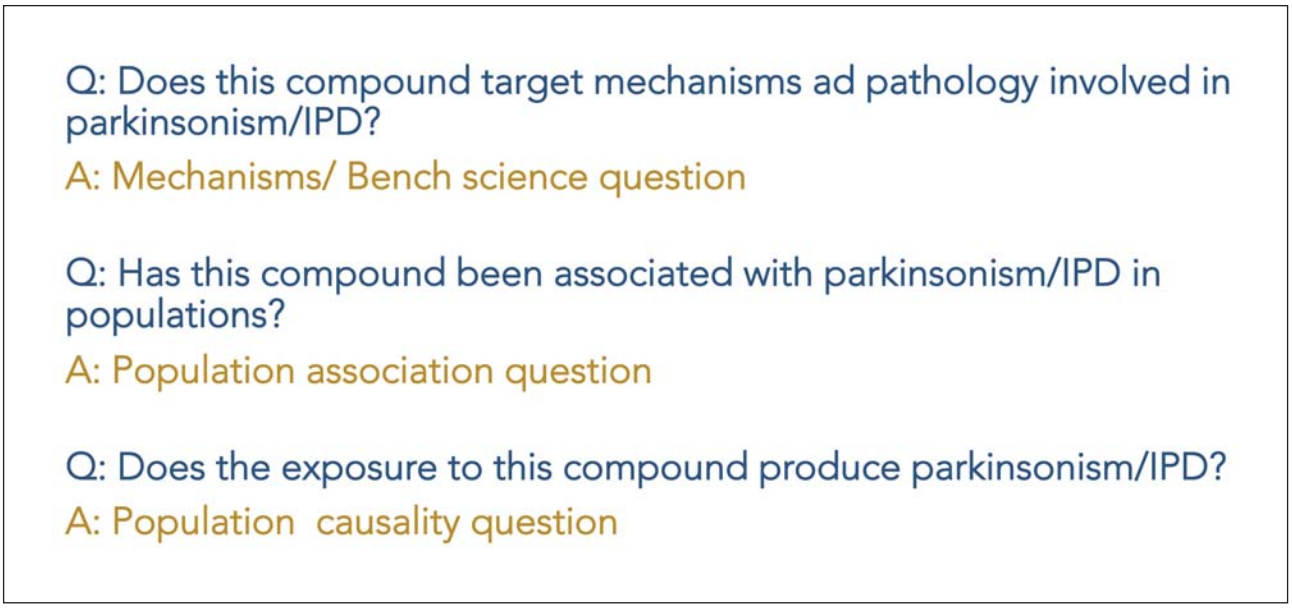

Figure 2. ***Three questions in the area of Parkinson's diseases (PD) Occupational Epidemiology***

hort of about seventy thousands employees of the Central Electricity Generating Board of England and Wales. All employees were hired in the period 1952-82. Detailed calculations had been performed by others to enable an assessment to be made of exposures to magnetic fields. No change in risk was revealed for the three main diseases neurodegenerative diseases as a consequence of exposure to magnetic fields (28).

The hypothesized mechanisms are different. Solvent and metals exposure play a role in the oxidative stress, mitochondrial toxicity and protein aggregation, and damage the cytoskeleton of long axons, resulting in a polyneuropathy (29,30), therefore the identification of markers of oxidative stress could be useful to distinguish normal biological processes from pathogenic one.

One if the challenges is the recognition and quantification of toxic exposure, especially because the exposure may last decades and the quantities involved may be small. Furthermore, occupational exposures to metals pesticides, organic solvents and electromagnetic fields are often mixed and difficult to determine the individual contribution (3). There are different layers of interconnected questions that can be answered in different settings with different study design (Figure 2).

The quality of toxic exposure identification especially over long period of time is really still inadequate. The use of both cohort and case control design both present problems when applied to the field of occupational epidemiology of neurodegenerative diseases.

Furthermore, there is need for experts in the field of pharmacology, neurosciences, clinical, chemistry, agrochemical companies, farmers and members of governmental regulatory agency to work together in the near future. The public health especially in the field of occupational epidemiology of NDG diseases needs an integrated approach that is recently renamed Convergence science. Convergence science is a transdisciplinary approach for framing research questions (31). Reimagining population health as convergence science lancet 2018 392: 367-8. From 5 to 20% of cancers are probably based on occupational exposures. It is not unconceivable hat we are in the same order for neurodegenerative diseases (3). Success in prevention in this as in other sectors will be possible only on new and strategic convergence across different domains from policies to basic science.

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