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ROLE OF PESTICIDES IN INTESTINAL DYSBIOSIS AND DEVELOPMENT OF NEURODEGENERATIVE DISEASES

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ABSTRACT

The analysis of recent literature on the correlation between intestinal dysbiosis and chronic degenerative diseases shows an increased risk of developing spondyloartropatia seronegative, chronic inflammatory bowel diseases, autoimmune diseases and neurodegenerative diseases (Alzheimer's, Parkinson's and Amyotrophic Lateral Sclerosis) in subjects suffering from dysbiosis. The aim of the study is, to investigate through a metanalysis, the existence of the causal relationship between the use of pesticides in the work environment and the development of neurodegenerative diseases and then to formulate a physiopathological model valid to explain the development of dysbiosis-induced neurodegeneration in subjects exposed to pesticides. A careful analysis of the studies produced that investigate the relationship between the use of pesticides and the development of intestinal dysbiosis and the relationship between the latter and the development of neurodegenerative diseases has been carried out. To reduce the scope of the study we decided to consider, among the various neurodegenerative diseases, exclusively Alzheimer's Dementia, Parkinson's disease and Amyotrophic Lateral Sclerosis (SLA). Examination of the results shows, an increased risk of neurodegenerative diseases and in particular Parkinson's, Alzheimer's and SLA, in subjects exposed to pesticides. Alzheimer's disease, Parkinson's disease and SLA all have common pathological characteristics. The hallmark of these neurological disorders is, in fact, protein misfolding (i.e. incorrect folding) and the consequent aggregation and deposition of proteins in the CNS with progressive neuronal loss. The condition of dysbiosis, favors the stabilization of an imbalance between bacterial strains producing intestinal amyloid and non-producing strains; this triggers the enhancement of the endogenous response to neuronal amyloids via the intestine-brain axis.

1. Introduction

The growing need to safeguard crop production and foodstuffs has led, over time, to a progressive increase in the use of pesticides in the agri-food sector; almost in parallel with this trend, epidemiological studies record the simultaneous increase in incidence and prevalence of neurodegenerative diseases.[5]

The term pesticide, in fact, undergoes a broader category of substances that also includes plant protection products used to prevent the destruction of plantations by weeds (molluscs, rodents, lichens) and/or the development of infectious diseases by viruses, bacteria, mycoplasmas and fungi, as well as to combat and eliminate weeds and unwanted plant species.

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These substances, interacting with microbial biosystems of the skin, oral cavity, respiratory tract, and gastrointestinal tract and, once absorbed, altering the biochemical-cellular processes of different organs and apparatuses, represent a risk factor for the health of exposed subjects.

The gut microbiota is a labile system that can be easily compromised by different physiological factors (age, genetic background and eating habits), pathological (infections, enzymatic defects) and iatrogenic (surgeries, antibiotics, antifungals, viral replication inhibitors, laxatives, chemotherapy and pesticides). Alterations to this complex ecosystem are involved in the pathogenesis of several immunologically based systemic diseases, such as rheumatological diseases, chronic inflammatory bowel diseases, metabolic syndrome, diabetes mellitus and neurodegenerative diseases.[6,7]

Under conditions of balance between the various microbial species, pathogenic and non-pathogenic, which make up the intestinal microbiota, an immunological tone of tolerance prevails at the mucosal level that contributes to the homeostasis of the mucous membrane of the colon;[8,9] this condition is known as eubiosis; the alteration of this microbial balance is defined as dysbiosis and is associated with a qualitative and/or quantitative proliferation of enteropathogenic germs. The effects due to the alteration of microbial homeostasis are very heterogeneous and range from local effects, primarily of a phlogistic and irritative type, to systemic effects potentially capable of creating the conditions suitable for the onset of numerous pathologies, even of a systemic nature.

The typical signs and symptoms of intestinal dysbiosis are constipation, diarrhea, irregular alvo, meteorism, abdominal pain, post-prandial swelling, aerophagia, disorders of the psychiatric sphere, increased susceptibility to infections and skin problems. However, the initial clinical manifestations of are more frequently nonspecific and concern the organ primarily involved or the colon. The result is that the physiopathological understanding of systemic clinical manifestations is more complex; for this reason, it is important to pay attention to the mechanisms underlying the abnormal and improper activation of the lymphatic system associated with the intestinal mucosa (GALT) that is observed in the course of dismicrobism and which plays a central role in the pathogenesis of numerous dysbiosis-related diseases. In particular, intestinal dismicrobism activates dendritic cells to produce proinflammatory cytokines that promote the differentiation of T cells into Th1, Th2 and Th17 effecting cells, resulting in suppression of T-regulatory cell differentiation (T-reg) and development of a local inflammatory process that constitutes the suitable substrate for the development of chronic systemic diseases.

2. Material and methods

The purpose of our study is to prove the existence of a causal relationship between the use of pesticides in the workplace and the development of neurodegenerative diseases as a function of the alteration of the intestinal microbiota in the exposed subjects and, at the same time, to formulate a functional model to explain the physiopathological mechanisms of dysbiosis-induced neurodegeneration.

We started with defining the concept of exposure to pesticides to exclude any interpretative biases related to environmental studies; for this reason, studies were considered in our analysis that included, exclusively, the subjects that, in relation to the direct use of the substance, could be considered exposed.

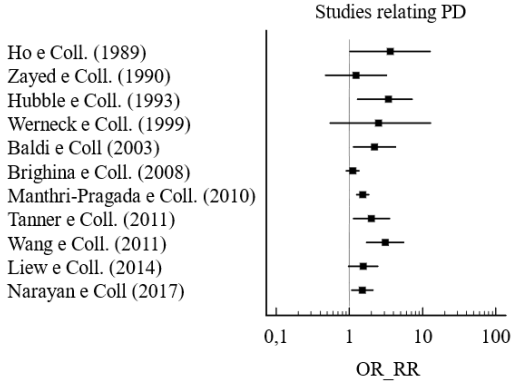
Therefore, defined the concept of exposure to pesticides, a detailed research of the data present in the literature was carried out through the analysis of studies that investigate the correlation between exposure to pesticides and the development of neurodegeneration. To narrow down the focus of the study, it was decided to consider, among neurodegenerative diseases, the most widespread and socially impactful: Alzheimer's Dementia, Parkinson's disease and Amyotrophic Lateral Sclerosis (SLA).

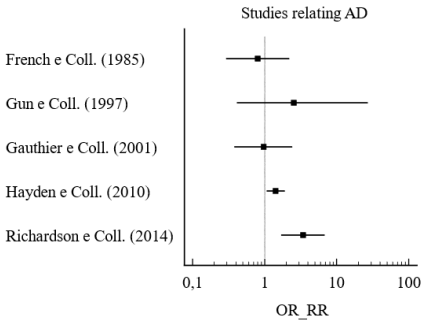
The research was conducted on Medline® through Pubmed® and the terms entered into the database for the research were: "Parkinson's", "Alzheimer's", "Amyotrophic Lateral Sclerosis" in cross combination with "pesticide", "insecticide", "herbicide", and "Glyphosate".

Given the number of studies present, it was initially carried out with the development of three metanalysis to confirm, through the selective extraction of the timely estimates of risk – Odds Ratio –and confidence intervals, the existence of the increased risk of developing neurodegenerative diseases in subjects exposed to pesticides. It was therefore decided to exclude reviews, editorials, studies not conducted in humans and those that did not estimate the risk or did not report the confidence interval at 95% (95% JV), while the studies included mainly case-control and cohort studies (Table 1).

Risk estimates were analyzed through statistical analysis software (MedCalc®) from which the respective Forest Plots were extracted (Figure 1).

Specific risk estimates show a fair heterogeneity which cannot be easily attributed to the methodological differences with which individual studies have been carried out (e.g. differences in the assessment of exposure to toxicity), but which is probably due to the absence of objective systems for assessing individual exposure to the toxic substance.





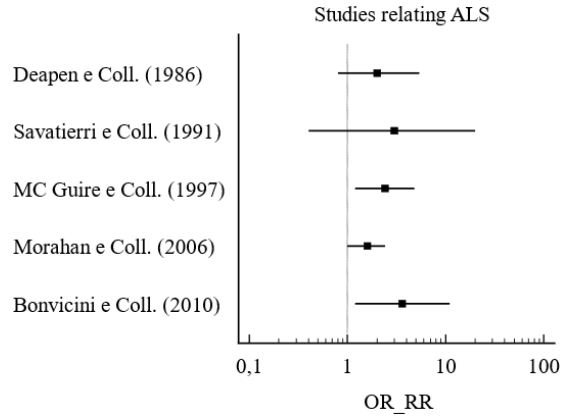


Figure 1. Risk estimates analyzed through statistical analysis software (MedCalc®) from which the respective Forest Plots were extracted. PD, AD and SLA odds ratio /relative risk estimates for any pesticide exposure from the analysis of the single odds.

	Authors	Types of studies	OR/RR (95%IC)
Studies relating to PD	Ho e Coll. (1989)	C-C	3,6 (1-12,9)
	Zayed e Coll. (1990)	C-C	1,23 (0,46-3,29)
	Hubble e Coll. (1993)	C-C	3,42 (1,27-7,32)
	Werneck e Coll. (1999)	C-C	2,49 (0,53-13,14)
	Baldi e Coll (2003)	C-C	2,20 (1,11-4,34)
	Brighina e Coll. (2008)	C-C	1,11 (0,89-1,38)
	Manthri-Pragada e Coll. (2010)	C-C	1,52 (1,23-1,89)
	Tanner e Coll. (2011)	C-C	2,00 (1,11-3.60)
	Wang e Coll. (2011)	C-C	3,09 (1,69-5,64)
	Liew e Coll. (2014)	C-C	1,55 (0,96-2,51)
	Narayan e Coll (2017)	C-C	1,50 (1,05-2,14)
Studies relating to AD	French e Coll. (1985)	C-C	0,80 (0,29-2,19)
	Gun e Coll. (1997)	C-C	2,54 (0,41-27,06)
	Gauthier e Coll. (2001)	C-C	0,97 (0,38-2,41)
	Hayden e Coll. (2010)	Co	1,42 (1,06-1,91)
	Richardson e Coll. (2014)	C-C	3,40 (1,70-6,82)
Studies relating to ALS	Deapen e Coll. (1986)	C-C	2,0 (0,8-5,4)
	Savatierri e Coll. (1991)	C-C	3,0 (0,4-20)
	MC Guire e Coll. (1997)	C-C	2,4 (1,2-4,8)
	Morahan e Coll. (2006)	C-C	1,6 (1,0-2,4)
	Bonvicini e Coll. (2010)	C-C	3,6 (1,2-11)

Table 1. The most important case-control and cohort studies relating Parkinson's disease, Alzheimer's dementia, Amyotrophic Lateral Sclerosis.

3. Results

The search in Medline and Pubmed yielded over 1000 publications; after a thorough analysis of these publications, studies included in the meta-analysis (Fig. 1) were the ones that evaluated occupational exposure to pesticides as a group, usually with some minimal criterion forever use, e.g., regular use and/or use for some minimal period. Race/ethnicity and voluptuous habits were similar in cases and controls (data not shown). Information on cumulative lifetime use of specific pesticides was limited.

There were 20 case-control studies and 1 cohort study and of these, 11 regarding the relationship between pesticides and PD, 5 regarding the relationship between pesticides and AD and 5 regarding the relationship between pesticides and SLA. Figure 1 shows PD, AD and SLA odds ratio /relative risk estimates for any pesticide exposure from the analysis of the single odds. From summary odds, it can be deduced that pesticides exposure represents a risk factor for the neurodegenerative diseases examined.

4. Discussion

Neurodegenerative diseases constitute a heterogeneous set of neurological diseases characterized by an irreversible and progressive loss of neuronal cells in some areas of the CNS. For many of them, the causes of onset are still unclear. However, a multifactorial physiopathological model is considered valid, so that among the risk factors recognized are those on a genetic and hereditary basis and those of an environmental type (xenobiotics). Recent studies also identify a common risk factor for the development of neurodegenerative diseases, namely intestinal dysbiosis.[10.11] It is known, in fact, that the intestinal microbiota has a key role in supporting the maintenance of homeostasis of the host organism, and in particular, the condition of eubiosis seems to guarantee the functioning of the mechanisms responsible for the maturation, development and maintenance of neuronal homeostasis.[11,12]

Several factors can influence the composition of the intestinal microbiota, favoring the development and maintenance of dysbiosis, among which are recognized modifiable factors and immutable factors; among the immutable factors, genetic factors are the most important, while among the modified ones include diet, antibiotics, and toxic substances such as pesticides.[13,14]

Pesticides can enter the human body through consuming food that contains chemical residues, as well as through contaminated water. Additionally, exposure can occur during the production and/or use processes. Although all pesticides, by toxicodynamic characteristics, are capable of determining dysbiosis, some of these have been described in the mechanisms and ways in which they interfere with the microbiota, among them: organophosphorus (Chlorpyrifos)[15], Glyphosate[16], Imidazolic derivatives (Imazalil)[18], Carbamates (Propamocarb)[17] and Benzimidazolic derivatives (Carbendazim).[19]

The existence of an increased risk of developing neurodegenerative diseases in those exposed to pesticides finds support in the three metanalyses that we have developed from studies present in the literature in order to include, exclusively, those who could be considered exposed to plant protection products given the actual use of these substances in the field of employment or non-employment. A careful analysis of the studies included to assess the actual existence of the risk shows limits in our assessment to be referred, probably, to the small number of residual studies included and the discrete heterogeneity from the risk estimates motivated by the absence of objective systems that allow to evaluate specifically and individually the individual exposure to the different pesticides. Considering the above limits, examination of the results expressed in forest plots shows that occupational and non-occupational exposure to plant protection products predisposes to the development of neurodegenerative diseases, particularly Alzheimer's, Parkinson's and SLA.

Therefore, clarified the concept that identifies plant protection products as a potential risk factor for the development of neurodegeneration and considering that they are responsible for the alteration of intestinal eubiosis, we can hypothesize that intestinal dismicrobism plays a role as a potential trigger factor for neurodegenerative diseases. Following this hypothesis and through a meticulous analysis of the studies in the literature, we have developed a physiopathological model that sees in the increase of intestinal permeability, the production of misfolded proteins and the alteration of the intestine-brain axis the critical elements of neurodegeneration.

The intestine-brain axis is a physiological two-way communication system between the brain and the enteric nervous system (SNE) or metasympathetic. The intestinal microbiota plays a key role in the processes of two-way bowel-brain interaction, modulating the maturation and functioning of immune cells and intestinal epithelium through the transduction of immunological signals to the metasympathetic system and, consequently, the central nervous system (CNS).[20] This allows, in light of new scientific knowledge, to overcome the already innovative idea of a brain-intestine axis and to consider the resident microbiota as a fundamental actor of this communication process in a complex system that becomes a microbiota-intestine-brain axis.

The central role of the microbiota in this cross-talk process is the basis of the mechanisms involved in etiopathogenesis and/or the progression of neurodegenerative diseases.

Understanding the link between intestinal dysbiosis and neuro-inflammation requires knowledge of the characteristics of the microbiota-brain-intestine axis and intestinal and hematoencephalic mucosal barriers (BEE).

In conditions of dysbiosis, competition between intestinal microbial species leads to an imbalance between non-amyloid-producing strains and producer strains in favour of the latter; this imbalance produces an excess of amyloid that interacts with toll-like receptors (TLRs) at the galt level and generates a local inflammatory response with functional alterations of tight-junctions and consequent increase in intestinal permeability. It is known that many gut microbial species produce amyloid proteins that share structural and biophysical properties with neuronal amyloid; interestingly, one of the most studied bacterial amyloids, Curlin, contains a repeated sequence of amyloid peptides, also shared by alpha-synuclein.[21-22]

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and SLA share a common histopathological feature, namely aggregation and deposition of altered proteins (misfolded) in the CNS. These proteins, represented by the β-amyloid protein, alpha-synuclein and tau protein, have cross-beta-sheet polymer structures similar to those of microbial-derived intestinal misfolded proteins. Studies on the aggregation and storage of amyloid proteins identify cross seeding, that is, that phenomenon for which different protein aggregates can act as a "core" substrate for the aggregation of other proteins, the mechanism through which amyloids of intestinal origin act as activists of the misfolding of proteins involved in neurodegeneration.[23]

Given the different studies reported in the literature, we have developed a four-step physiopathological model, which allows us to explain how intestinal dysbiosis correlates with pathogenic events that lead to the degeneration of nerve cells.

The first phase is characterized by the development and stabilization of an imbalance between amyloid-producing intestinal bacterial strains (overexpressed during dysbiosis) and non-producing strains, resulting in the overproduction of misfolded amyloid proteins (M-proteins) that precipitate and accumulate at the level of Peyer's lymphatic follicles, triggering a local inflammatory response.

The next phase of promotion sees the chronicity of the phlogistic stimulus due to the continuous production of M-proteins and the induced de-regulation of the immunoregulatory mechanisms of innate immunity, increasing intestinal permeability.

This increase in intestinal permeability allows the subsequent spread in the blood cycle of toxic substances deriving from metabolic processes and M-proteins, triggering a systemic inflammatory process that also favors the loss of BEE integrity and the spread of M-proteins of intestinal origin in the CNS. Here, M-proteins act as core proteins that, through a cross-seeding process with proteins of neuronal origin, determine, in the latter, the acquisition of a cross-beta-sheet conformation favoring precipitation and accumulation in nerve cells.

Finally, the last phase sees the apparent damage as a consequence of the chronic inflammatory process in response to neuronal amyloids and the consequent development of degenerative phenomena.

5. Conclusions

Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis are neurological diseases that have common pathological characteristics. The hallmark of these neurological disorders is protein misfolding, resulting in protein aggregation and deposition in the CNS and progressive neuronal loss.

Taking into account the above, and based on the data obtained from experimental models that have recently found flourishing development on the international scientific scene and that produce a vast scientific literature on the subject, we can hypothesize that intestinal dysbiosis secondary to exposure to pesticides is one of the most crucial moves in the development of neurodegenerative diseases in professionally exposed subjects. We also believe that pesticide-induced dysbiosis is a fertile substrate for developing neurodegenerative diseases in the non-working/non-professionally exposed population due to the residue of active substances in processed foods directly and indirectly (residue in animal meat) and environmental pollution.

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References

1.Horta-Baas G, Romero-Figueroa MDS, Montiel-Jarquín AJ, Pizano-Zárate ML, García-Mena J, Ramírez-Durán N. Intestinal Dysbiosis and Rheumatoid Arthritis: A Link between Gut Microbiota and the Pathogenesis of Rheumatoid Arthritis. J Immunol Res 2017;2017:4835189.

2. Jiang C, Li G, Huang P, Liu Z, Zhao B. The Gut Microbiota and Alzheimer's Disease. J Alzheimers Dis 2017;58:1-15.

3. Claus SP, Guillou H, Ellero-Simatos S. The gut microbiota: a major player in the toxicity of environmental pollutants?. npj Biofilms and Microbiomes 2016;2:16003.

4.Walker LC, Schelle J, Jucker M. The Prion-Like Properties of Amyloid-beta Assemblies: Implications for Alzheimer's Disease. Cold Spring Harb Perspect Med 2016; 6(7): a024398.

5.Reitz C, Brayne c, Mayeux R. Epidemiology of Alzheimer disease. Nat Rev Neurol 2011;7:137-52.

6. Li X, Watanabe K, Kimura I. Gut Microbiota Dysbiosis Drives and Implies Novel Therapeutic Strategies for Diabetes Mellitus and Related Metabolic Diseases. Front Immunol 2017 Dec 20;8:1882.

7. Westfall S, Lomis N, Kahouli I, Dia SY, Singh SP, Prakash S. Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis. Cell Mol Life Sci 2017 74:3769-3787.

8. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell 2006;124:783- 801. 29.

9.Ardizzone S, Bianchi Porro G, The topical treatment of distal ulcerative colitis. Eur Gastroenterol Hepatol 1996;8:599-602.

10. Sun F, Shen YQ. Dysbiosis of gut microbiota and microbial metabolites in Parkinson's Disease. Ageing Research Reviews 2018;45:53-61.

11. Dinan TG, Cryan JF. Gut Instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration. J Physiol 2017; 15;595:489-503.

12. Tomasello G, Zeenny MN, Giammanco M, Di Majo D, Traina G, Sinagra E, Damiani P, Zein RJ, Jurjos A, Leone A. Intestinal microbiota mutualism and gastrointestinal diseases. EuroMediterranean Biomedical Journal 2015;10:65-75.

13.Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, Harris HM, Coakley M, Lakshminarayanan B, O'Sullivan O, Fitzgerald GF, Deane J, O'Connor M, Harnedy N, O'Connor K, O'Mahony, vanSinderen D, Wallace M, Brennan L, Stanton C, Marchesi JR, Fitzgerald AP, Shanahan F, Hill C, Ross RP, O'Toole PW. Gut microbiota composition correlates with diet and health in the elderly. Nature 2012;488:178-184.

14.Jernberg C, Löfmark S, Edlung C, Jansson JK. Microbiology-Long-term impacts of antibiotic exposure on the human intestinal microbiota. Microbiology 2010; 156: 3216-23.

15.Joly C, Gay-Queheillard J, Leke A, Chardon K, Delanaud S, Bach V, Khorsi-Cauet H. Impact of chronic exposure to low doses of chlorpyrifos on the intestinal microbiota in the Simulator of the Human Intestinal Microbial Ecosystem (SHIME®) and in the rat. Environ Sci Pollut Res 2013;20:2726-34.

16. Samsel A, Seneff S. Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance. Interdiscip Toxicol 2013;6:159-184.

17. Jin C, Zeng Z, Fu Z, Jin Y. Oral imazalil exposure induces gut microbiota dysbiosis and colonic inflammation in mice. Chemosphere 2016;160:349-358.

18. Wu S, Jin C, Wang Y, Fu Z, Jin Y. Exposure to the fungicide propamocarb causes gut microbiota dysbiosis and metabolic disorder in mice. Environmental Pollution 2018; 237:775-783.

19. Jin Y, Zeng Z, Wu Y, Zhang S, Fu Z. Oral Exposure of Mice to Carbendazim Induces Hepatic Lipid Metabolism Disorder and Gut Microbiota Dysbiosis. Toxicological Sciences 2015:147:116-126.

20. Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. Nature Neuroscience 2017;20:145-155.

21.Chapman MR, Robinson LS, Pinkner JS, Roth R, Heuser J, Hammar M, Normark S, Hultgren SJ. Role of Escherichia coli curli operons in directing amyloid fiber formation. Science 2002; 295:851-5.

22.Cherny I, Rockah L, Levy-Nissenbaum O, Gophna U, Ron EZ, Gazit E. The formation of Escherichia coli curli amyloid fibrils is mediated by prion-like peptide repeats. J Mol Biol 2005; 352:245-252.

23.Chen SG, Stribinskis V, Rane MJ, Demuth DR, Gozal E, Roberts AM, et al. Exposure to the Functional Bacterial Amyloid Protein Curli Enhances Alpha-Synuclein Aggregation in Aged Fischer 344 Rats and Caenorhabditis elegans. Sci Rep 2016; 6:34477.