WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 14, 566-574. Review Article ISSN 2277– 7105

ROLE OF PESTICIDES IN THE PATHOPHYSIOLOGY OF PARKINSON'S DISEASE AND ITS AYURVEDA PERSPECTIVE

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Article Received on
05 October 2021,

Revised on 25 October 2021,
Accepted on 15 Nov. 2021

DOI: 10.20959/wjpr202114-22333

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ABSTRACT

Background: A person's genetic makeup is likely more important in determining whether he or she develops Parkinson's disease than any environmental risk factor. PD is a neurodegenerative disorder, affecting greater than 1% of the worldwide population over the age of 65 and is the fourth most common neurological degenerative disorder found in the elderly. Environmental factors have been shown to contribute to the incidence of PD. Pesticides, which represent one of the primary classes of environmental agents associated with PD, share the common feature of being intentionally released into the environment to control or eliminate pests. There is a strong bond between the pesticides and the occurrence of Parkinson's disease. **Methodology:** All the available information was collected from available text books and digital sources. **Discussion:** *Kaphavruta vyana* shares the same platform with the Parkinson's disease in majority of the time. The concept of cumulative toxicity (*Dushi Visha*) of *Ayurveda* says about slow acting poison which are not been completely eliminated out of the body. After retaining for a longer period of time in the bodily tissues, this latent poison does contamination. The route of entry of these harmful substances, after entering into the body, accumulates and not eliminated from the body. This accumulation at the level of system does the chronic poisoning and related symptoms too, which are seen on both body and mind. **Conclusion:** Parkinson's disease is caused by combination of factors. Better understanding of complex genetic, environmental, aging and other factors lead to Parkinson's would be a game changing in our pursuit of preventive and therapeutic options. The study Parkinson's disease under the pathology of

cumulative toxicity may provide a new lanein the treatment aspect.

KEYWORDS: Parkinson's disease, neurodegenerative, *Kaphavruta Vyana Vata, Dushi visha,* Cumulative toxicity.

INTRODUCTION

Parkinson's disease (PD) is a chronic progressive disease of the neuro-degenerative disease characterized by the cardinal features of rigidity, bradykinesia, tremor and postural instability. It is affecting greater than 1% of the worldwide population over the age of 65 and is the fourth mostcommon neurological degenerative disorder found in the elderly.[1]

In India, the crude age adjusted prevalence rate of Parkinson's disease per 100,000 population is 14 in northern India, 27 in the southern India and 16 in the eastern part of India.[2]

A person's genetic makeup is likely more important in determining whether he or she develops Parkinson's disease (PD) than any environmental risk factor. This is probably the case even in a person without a known family history of PD. However, environmental exposure may be important in triggering the disease in a person genetically susceptible to it. There are more thanlikely that additional chemicals in our environment, ones that haven't yet been studied and which may increase the risk of PD. Pesticides, which represent one of the primary classes of environmental agents associated with PD, encompass an array of compounds designed to deter or kill insects (insecticides), rodents (rodenticides), plants (herbicides) and fungi (fungicides). The impact of pesticide exposure has become a globally developing environmental health problem. Although PD existed long before the introduction of these pesticides, the thought is that pesticide exposure has contributed to the increased incidence of the disease. The term *Dushi Visha*[3] is a combination of two different words, '*Dushi'* and *'Visha'*. *'Dushi'* means denatured, attenuated, latent, vitiated. *Visha* means poison. *Dushi Visha* means denatured poison or attenuated poison. *Acharya Susruta* and *Vagbhata* described *Dushi Visha* as any kind of poison originating from inanimate or animate sources or any artificial poison (*KritrimaVisha*) retained in the body after partial expulsion by the anti-poisonous drugs, is termed latent poison (*Dushi Visha*).[4,5] Any poison that is incapable of producing acute symptoms of poisoning can also be designated *Dushi Visha.* Because of the low potency of the poison, it usually not capable to cause sudden death. Because of the enveloping *(Avarana)* action by *Kapha dosha*, these low potency poisons are

retained in the body for a long period without producing any grave or fatal symptoms.[6] *Dushi Visha* plays an important role in causing parkinsons disease.

Kaphavruta vyana[7] shares the same platform with the Parkinson's disease in majority of the times. The goal of this review is to understand the literature and to analyse those subclasses of pesticides which are associated with PD and their strength to cause PD.

Pathophysiology of pesticide causing PD

Pathologically, PD is characterized by a progressive loss of dopamine neurons in the substantia nigra pars compacta (SNpc), a loss of dopamine input to the striatum, the presence of ubiquitin and α-synuclein-positive cytoplasmic inclusions known as Lewy bodies,[8] depigmentation of the locus ceruleus and autonomic dysfunction including sympathetic denervation of the heart.[9] The loss of dopamine is responsible for the majority of the motor symptoms of PD.

The chemical with the most data linking it to an increased PD risk is paraquat,[10] with exposure associated with a 2-3fold of increased PD risk over the general population. It's mechanism of action is the production of reactive oxygen species, intracellular molecules that cause oxidative stress and damage cells. It also causes loss of nigral dopamine neurons and degeneration of striatal terminals, as well as decreased locomotor activity.[11] it is highly toxic quaternary nitrogen herbicide, not readily absorbed from the GIT and is poorly metabolized. It can be transported across the blood-brain barrier by the action of a neutral amino acid transporter carrier such as the system L-carrier (LAT-1) which normally carries amino acid L–valine and L –phenylalanine.[12]

The fungicide maneb,[13] the overlap in geographic usage of these compounds was used as a rationale for animal studies that showed that theexposure caused decreased motor activity, alteredstriatal dopamine and dopamine metabolites, decreased striatal tyrosine hydroxylase and dopamine transporter (DAT) expression and increased accumulation of dopamine in synaptosomes.[14]

It has been shown to induce oxidative stress, α – synuclein aggregation due to proteasomal dysfunction. Stimulation of free radical production, pesticide could also activate glutamatergic neurons leading to the activation of NMDA receptors & further generation of free radicals resultingin neuronal degeneration.[15]

Rotenone and other rotenoids are highly toxic, naturally occurring botanical pesticides.[16] Rotenone is very hydrophobic and, thus, easily can cross biological membranes without the need for a transporter. It has poor bioavailability and has a short half-life in the environment. Because of the known systemic inhibition of mitochondrial complex, I (NADH dehydrogenase) in PD patients,[17] the possibility of rotenone, also a complex I inhibitor, being an environmental contributor to PD has been extensively examined. Some early studies with rotenone exposure found minimal nigrostriatal damage[18] or found damage to striatal dopamine fibers. Studies showed that chronic and subcutaneous administration of rotenone could result in a parkinsonian syndrome with selective dopamine neuron degeneration, oxidative damage and cytoplasmic inclusions reminiscent of early Lewy bodies.[19]

Dushi visha

Dushi Visha a slow potency poison or when all poison which not completely eliminated from the body or partially detoxified due to incomplete metabolism. It loses its original properties and gets converted into low potency poison due to some conjugation and after the secondary cause, itproduces various disorders.[20]

"कालान्तर प्रकोपि विषं दुषिविषम् ॥" (चक्रपाणि) (च.चि.२३)

Factors that aggravate *dushi visha*[21]

"दूषितं देशकलान्नदिवास्वप्नैर्भिक्षणश : | यस्मद्दुषयेत धातूनतस्मदुषिविषं स्मृतम ॥" (सु. क. २/३३)

- ***Dooshita desha*** – *Dalhana* explains that *Anupa Desha* where there will be excess of wind, cold weather and increased rainfalls are present. Such land i.e., *Anupa Desha* influences on *Kapha* and *Vata dosha* and leads to the aggravation of *Visha* in the bodyas latent poison or *Dushi Visha*, which is weaken by *Kapha dosha*.
- ***Dooshita Kala and Anna*** - Kala can be understood as *Sheeta Anila* or cold wind and *Durdina* or on cloudy days, which may have relation with latent poison (*Dushi Visha*). Rain makes body moist (*Klinna*), cold wind reduces the *Pachakagni* hence metabolism reduces and improper metabolism leads to the derangement of detoxification which finally leading to the aggravation of both *Kapha and Vata Dosha.*
- **Among 7 *sthavara visha vega,*[22]** *lakshans* which produced by *visha* are similar as thatof Parkinson's disease.
- 1st – *stabdhaa*
- 2nd – *vepathu*

- 5th – *parvabeda*
- 6th – *pragnya* & *praana bhrusham*
- 7th – *skandh, prushta, kati bhanga*

Concept of *ama*

The corruption & interaction of vitiated *dosha* gives rise to just as *kodrava dhanya* which produces toxic material due to the influence of *Desha, Kala*, etc.[23]

"अन्ये दोषेभ्य एवाति दुष्टेभ्यो अन्योन्य मूर्च्छनात् ।
कोद्रवेभ्यो विषस्येव वदन्त्यामस्य संभवम् ॥ " (अ.सं.सु २१/३५)

When there is *Ama* formation due to improper digestion because of *Pachakagni mandya*,will give rise to the *lakshanas* like that of parkinson's disease.

सामलक्षण:

"स्रोतोरोध **बलभ्रंश** गौरवानिल मूढता । आलस्य अपक्तिं निष्ठीव **मलसङ्ग** अरुचि क्लमः ॥
लिङ्गं मलानां सामानां निरामाणां विपर्ययः ।" (अ.हृ.सू.११)

Concept of *avarana*

The symptoms of Parkinson's disease mimic the *lakshanas* of *Kaphavruta Vyana vata* and *Shleshmavruta Udana vata. Vak - swara graha, dourbalya*[25] are the *lakshanas* and *Gati sanga*[26] being the main *lakshana* which means there will be great impairment in walking in a patient ofParkinson's disease.

"कफावृत व्यान गुरुतां सर्वगत्राणा सर्व संध्यस्थिरुजः ।
व्याने कफावृते लिङ्गं **गतिसङ्गःस्तथाधिकः** ॥ " (च.चि. २८/२२८)

DISCUSSION

Based on several comprehensive epidemiological studies, Pesticide exposure does appear to be a risk factor for PD. It has existed for centuries; pesticides are obviously not the sole cause of the disease. However, if one considers these compounds as accelerators or promoters of PD pathogenesis, we can begin to explain why the association with PD might arise continually and why it might not always be consistent.

Exposure at some point during the pathogenesis, which has been suggested to occur over the course of decades, could accelerate the underlying neurodegenerative process. However, such compounds might not initiate the disease process, such that without other genetic or metabolic riskfactors they might be innocuous. Several of the compounds associated with PD have long

half- lives in the environment and in the body. This allows them to bioaccumulate and to exert adverse effects over extended periods of time.[27] Coupled with plausible mechanistic risks to the nigrostriatal dopamine system, such compounds could produce subtle toxic effects, but when these occur over the course of decades their cumulative effects could lead to an accelerated course of a progressive disease.[28] These compounds might individually and collectively increase the likelihood of dopamine cell death and increase the risk of reaching the critical pathophysiologicalthreshold at which PD symptoms become clinically visible.

Studies shown that rotenone is complex I inhibition and mitochondrial dysfunction in PD pathogenesis, whereas paraquat has provided insight into the role of oxidative stress in the disease. Given their ability to reproduce features of PD in animals, these compounds have been especially beneficial in understanding the events that lead to dopamine neuron cell death.[29]

Acharya Chakrapani explains in his commentary as, the poison, which gets aggravated after a long time is latent poison or *Dushi Visha*. In *Madhukosha* commentary on *Madhava Nidana* author has given some clarifications regarding *Dushi Visha*. *Sheeta anila* or cold breeze, cloudy days or *Durdina* are considered as aggravating factors of *Dushi Visha* as they aggravate *Kapha dosha*, and latent poison or *Dushi Visha* is covered *(Avrita)* by *Kapha*.

In our classics, the etiological factors of *Vata Vyadhi* are explained. Parkinson's disease resembles the *Kaphavruta Vyana* and *Udana* in many stages of the disease. *Chalatva* is the *Prakruta karma* of *Vata* which is being normally contributed by the equilibrium in the *gunas* of *Vata dosha* such as *rooksha*, *sheeta*, *laghu* etc. *Cheshta* and *gati* are the *prakruta karma of vyanavata*[30] and bala is the contribution of *Udana Vata.*[31] In Parkinson's disease, both the functions of *Udana* and *Vyana vata* seems to be deranged. As for the status of *doshas*, it is concerned it is seen that for the symptoms of this disease to manifest, *Vata* is *vriddha* or *kupita, Pitta* is *ksheena* and *Kapha* is *vriddha* and *kupita* again. The *Dushita dhatu* is *rasa* i.e., *rasakshaya*. The *updhatus* involved in the pathology are *snayu* and to an extend *sira*.

Here, the *avruta dosha* is *kapha* and the *avaraka* are the *Udana vata and Vyana vata*. *Cheshtahani* as well as *gatisanga* are the features of *Kaphavruta Vyana*. Postural instability is also the manifestation of *Kaphavruta Udana. Vak-graha* or dysarthria is seen in both *Kaphavruta Vyana* and *Udana.* In the later stages of the Parkinson's disease, higher mental functions, mainlymemory is impaired and also cognitive and mood disturbances are on the rise.

Here we can assumethe involvement of *Prana Vata*[32] in the *Samprapti* in this stage.

Kaphavarana to the *Dushi visha* reduces the potency of *ushna, Sukshma, Rukshadi gunas* of *Visha*. Because of *Kapha dosha Avarana, Agnimandya* and *Dhatwagnimandya* occurs which in turn leads to *Apakata* of *Dushi Visha* and which stays for longer time in the body without producingany signs and symptoms.

In our *Shastras*, it is very well told that any kind of poison or *visha* irrespective of *Sthavara, Jangama* and *Kritrima* (artificial poison) will attain a stage called *Dushi Visha* after they deprivation of their potency to some extent or if they are improperly expelled or partially detoxifiedfrom the body. Present food habits, life style and mental attitudes etc. are entirely different from that of the past. The basic essentials of life air, food and water are all polluted. These factors influence on causing the diseases.

CONCLUSION

Living in a modern society means being exposed to a variety of chemicals whose risks we don't completely understand. Among the harmful chemical substances, pesticides are more in common consumption or inhalation by humans producing Parkinson's disease although the PD existed before the usage of pesticides. Pesticides can change gene expression through a broad arrayof gene regulatory mechanism. Important mechanism of these chemicals is the alteration of gene expression mediated by chronic or low dose of pesticide for decades.

While it's impossible to eliminate all exposure to toxins, we can increase the awareness of what we are potentially being exposed to, and how we can limit the exposure.

The pathophysiology of PD in Ayurveda has unique approach with concept of *Avarana* of *Vata* with *Kapha Dosha*. Identifying improved methods of measuring exposure, such as biomarkers and earlier detection of PD could greatly facilitate progress in the field.

The concept of *Dushi Visha* is not clearly explained in many of Ayurvedic shastras. Certain points need clarification like; the topics that can be considered under the heading of *Dushi Visha* or its extent. It is felt that this is the proper time to consider these factors and understand their potency in the manifestation of diseases. As *hetu* is prime factor, as a primary step management *Nidana Priavrajana chikitsa*[33] should be adopted for forthcoming disease and also, *Rutu Shodhana* will help to detoxify the body.

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