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Link Between Chronic Pesticides Exposure And Occurrence Of Parkinson Disease In Reckless Farmers

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Abstract:

In the recent era, for the production of more crops with low labor, excessive and multiple pesticides are used by farmers. The objective of this study was to investigate the relationship between pesticides exposure and Parkinson disease (PD) in reckless male farmers. For this purpose 500 farmers and 500 control participants were recruited randomly from district Lower Dir, Khyber Pakhtunkhwa, Pakistan. A special questionnaire was prepared regarding their occupational activities, socio-demographic and clinical characteristics. In farmer's group, the numbers of people affected from PD (n= 8) and action tremors (n= 9) were high as compared to age matched control group (action tremor= 1). Therefore it is concluded from our study that chronic pesticides exposure in farmers can induce neurotoxicity and can lead to PD.

KEY WORDS:

Parkinson, Pesticides, Action tremor, Neurotoxicity.

INTRODUCTION:

Parkinson's disease (PD) is a late onset disorder of nervous system and occurs as a result of detoriations of substantial nigral dopaminergic neurons and formations of fibrillar cytoplasmic inclusions, called Lewy bodies that comprises of α-synuclein and ubiquitin. PD is characterized by four cardinal signs: postural instability, rigidity, chronic progressive tremors and bradykinesia [1-2]. In familial PD, rare cases of PD have been found to be associated with mutations in DJ-1, PINK1, LRRK2 and UCH-L1, encoding parkin and α-synuclein. For the very commonly occurring sporadic form of PD, the cause is unknown and the role of genetics is uncertain in such cases [3-4]. PD is an idiopathic disease, although a number of environmental factors play a crucial role. A number of meta-analysis of such studies, comprising 14 for pesticides exposure, 11 for farming, 18 for drinking well water and 16 for rural residence, considered that, all these are risk factors for the pathogenesis of PD development [5-6]. Besides pesticides exposure, milk consumption, certain occupations and head trauma increases the risk for PD [7]. The by-product of illicit heroin synthesis, 1- methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) was identified in human as a culprit for the induction of Parkinson disease [8]. The structural similarity between a common herbicide, 1,1′-dimethyl-4,4′-bypyridinium (paraquat) and the active metabolite of MPTP, 1-methyl- 4-phenylpyridinium ion (MPP+) prompted the possibility that paraquat might be a dopaminergic neurotoxicant [9-10]. Similarly rotenone also produces PD like damage in animal models by acting on the

nigrostriatal dopaminergic system [11]. Because of the high toxicity of pesticides, in UK and other European countries, pesticides such as dieldrin and DDT have been banned while for paraquat and rotenone the authorization for the manufacturing and utilizations have been withdrawn [12]. Exposure to different pesticides such as, diazinon, malathion, parathion, maneb, pyrethroids, carbamate, paraquat, DDT, organophosphatase and organochlorine are positively associated with PD development. In present time pyrethroids, carbamates and organophosphatase are very widely used all over the world [13]. Dithiocarbamate-based fungicides possess dopaminergic neurotoxicity because, it has been reported that maneb, a fungicide belongs to this class can develop Parkinsonism in humans [14-15]. Similarly during neonatal stage, exposure to paraquat and maneb increases the susceptibilities of nigrostriatal dopaminergic system during adulthood [16]. Rotenone, an insecticide is suggested as a neurotoxin because it inhibits mitochondrial complex 1 specifically. For idiopathic PD, mitochondrial complex 1 defect is well reported [17]. Organophosphorus insecticides including, chlorpyrifos and dichlorvos can develop PD, by reducing catecholamine and motor activity [18]. The UK pesticides action network has listed a total of 101 pesticides as hormone disruptors [19] because; they interfere with the synthesis, transport metabolism and elimination of hormone [20].

Approximately 5 billion hectares of the world's land surface ($\approx$38%) are used as agricultural lands, and since the 1950s, pesticides have been increasingly used to protect crops [21]. Approximately, 750 thousands chronic illness, 220 thousands fatal and more than 26 million non-fatal cases of pesticides poisoning results from the application of 3 million tons of pesticides each year [22-23]. For the sake of more food productions, the demand for new, potent and high amount of pesticides are increasing day by day. Only in Europe, approximately 140, 000 tons of pesticides are used annually for agriculture purpose. In the last 20 years, the use of pesticides for agriculture has grown 150% from 14.48 tons to 37.5 thousand tons [24]. Birds frequently use agriculture lands and are therefore commonly used as indicators of the pesticides toxicity [25] because; they are highly sensitive to their cholinesterase-inhibition effects [26]. Each year in USA, a mean of 1,237 documented birds are killed due to parathion, diazinon, monocrototophos, endosulfan, carbofuran and fenthion [27-28]. To these potent and new pesticides farmers are directly exposed in Pakistan because, they do not use any protective coverings like eye glasses, mask gloves and other coverings during fumigations. Their clothes and whole bodies are completely washed by pesticides during fumigation. They even do not wash their hands with soap after fumigation and drink water and take their breakfast or lunch in their fields. Most of them are snuff addicted which, during fumigation are contaminated by pesticides. These farmers also pollutes the main water supply (tube well), which are used for drinking. These reckless farmers are exposed to these pesticides from generations to generations [29].

In Pakistan, the awareness about the hazardous effects of pesticides exposure is lacking. Not only their bodies, food but their drinking water is also exposed to pesticides. The objective of this study was to analyze the association between persistent pesticides exposure and PD development in these reckless farmers.

MATERIALS AND METHODS:

Inform consent:

Before starting the study, an informed consent was signed from the entire participants.

Study area:

The study participants were recruited from district Lower Dir, Khyber Pakhtunkhwa, Pakistan.

Pesticides used in study area:

Most commonly pesticides used in study area are endosulfon, atrazine, nicosulfuron, pendimethaline, MCPA, bromoxynil, thiophanate methyl, imidacloprid, pyrimethanil, levofenoron, dimethomorph, pyraclostrobin, metiram, hexythiazox, chlorothalonil, nitonpiram, tebuconazole, cypermethrin, metalaxyl, cymoxanil, Mancozeb etc. They are also reported by Ghulam et al., [29].

Study design:

Two groups were made; control and farmers. Each group contained 500 participants. Control

group were totally not exposed to pesticides. They were healthy. The age ranges for both groups were from 55 to 70 years. These farmers have a history of more than 20 years of farming without using any protective clothing like mask, gloves etc. A specific questionnaire was designed regarding PD. The questionnaire administered is given as Table 1.

Table 1: Questions asked of the groups, control and farmers

Q. No.	Questions asked
1	Is there any difficulty while sitting and standing up from the chair or bed?
2	Is yours voice become too soft?
3	Is yours balance weak?
4	Is there any change in yours face expression (mask shape)?
5	Are there tremors in yours hands and feet?
6	Is there swinging of yours arms while walking?
7	Is there any rigidity in yours hands, feet and neck?
8	Are you stepping slowly?
9	Is there insomnia mean lack of sleep or less than 4 hours sleep per day?

Exclusion criteria:

Participants with familial PD, history of trauma or very ill were excluded from the study.

RESULTS:

The results showed that in farmers; tremors, insomnia, rigidity, arms swinging, alterations in face expressions (mask shape), voice alterations and weak balance were common as compared to age matched control group. In farmers in addition to slow stepping there were also problems during sitting and standing up from the bed or chairs as compared to control group. In farmers, 08 were diagnosed PD patients and 09 were suffering from action tremors. No such disordered were reported in control group. Table 2 is showing the summary for the questions included in questionnaire. Figure 1 is depicting graphical presentation of all the summary of the results. Table 3 is showing the summary for PD and action tremors (Figure 2). Figure 3 and 4 are showing the percentages for questions included separately.

Table 2: Showing all questions of the questionnaire from both the groups

	Farmers				Control			
	Yes	**%age**	**No**	**%age**	**Yes**	**%age**	**No**	**%age**
Q1	409	81.8	91	18.2	302	60.4	198	39.6
Q2	30	6	470	94	10	2	490	98
Q3	70	14	430	86	25	5	475	95
Q4	38	7.6	462	92.4	13	2.6	487	97.4
Q5	17	3.4	483	96.6	2	0.4	498	99.6
Q6	13	2.6	487	97.4	2	0.4	498	99.6
Q7	12	2.4	488	97.6	0	0	500	100
Q8	25	5	475	95	8	1.6	492	98.4
Q9	55	11	445	89	15	3	485	97

Table 3: summary for PD and Action Tremors

	PD	Action Tremors
Farmers	8	9
Control	0	1

DISCUSSION:

In the present study we found that PD and action tremors are very common in farmers as compared to age matched control group. Our findings are in agreement with the results of JM Gorel et al., 1998 who concluded that farming and occupational exposure to insecticides and herbicides are linked with the development of PD [30]. In PD patients, dopaminergic cell death in the substantia nigra may occurs either due to reduced mitochondrial activity, dysfunctions of lysosomal and proteosomal system and aggregation of alpha-synuclein [31]. There are three types of mechanisms that link pesticides exposure and PD development. The simplest is that, pesticides induce mitochondrial toxicity. Another mechanism is the inhibition or induction of enzyme that has a role in the transport and metabolism of xenobiotics [32]. Pesticides such as paraquat induces PD like symptoms such as, rigidity, postural instability, slowness of movements and tremors by depleting dopaminergic neurons in substantia nigra [33]. Paraquat can cross blood brain barrier (BBB) and accumulates in the brain. Paraquat in the substantial nigral dopaminergic neurons can synthesize intracellular reactive oxygen species (ROS) leading to production of protein carbonyls, malondialdehyde and DNA fragmentation. All these leads to inhibition of mitochondrial complex I, causes pertub mitochondrial respirations that ultimately leads to impair energy metabolism [34]. Similarly rotenone also crosses BBB and can inhibit the mitochondrial complex I of the electron transport chain leading to ROS generation, ATP (adenosine triphosphate) depletion and destructions of dopaminergic cells [35]. Rotenone also inhibits microtubules synthesis, depletes glutathione, aggregates α-synuclein and produces Lewy bodies leading to PD development [36]. A widely used fungicide, maneb induces dopaminergic neurotoxicity by inhibiting the activity of complex III in mitochondrial respiratory chain or facilitating catecholamine oxidation. Recently maneb was infused into the lateral ventricle of rat and induces neurotoxicity [15, 37]. Similarly dieldrin, an organochlorine pesticide produces neurotoxic and dopamine depleting effects by producing ROS formations, lipid peroxidation and by promoting a-synuclein fibril formation [35, 38]. Cyclodiene alter striatal dopaminergic activity both in vitro and vivo by inducing oxidative damaged [39].

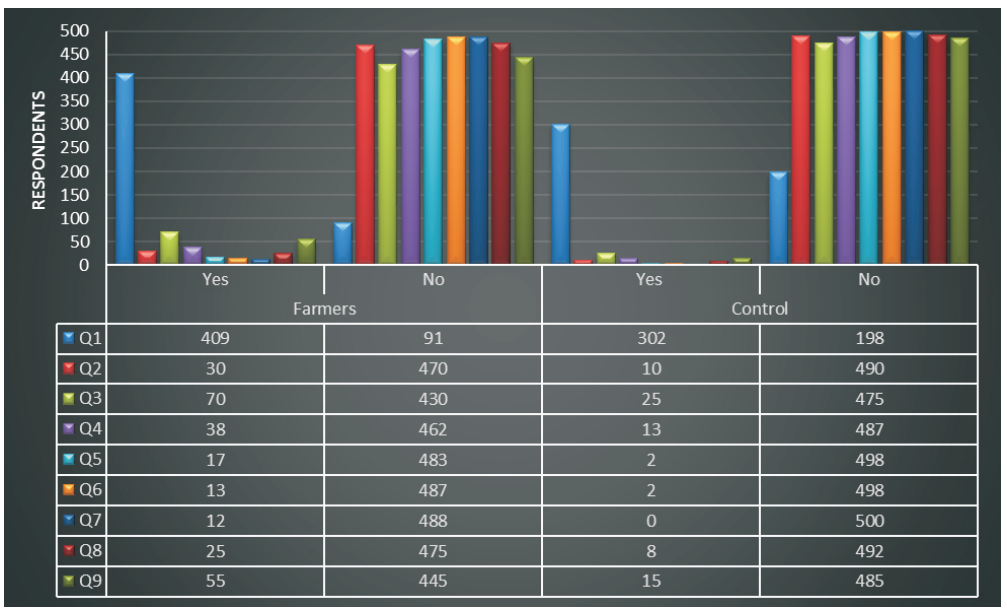


Figure 1: Showing all questions asked from both the groups (Farmers and Control)

In mammals and insects, organophosphates and methylcarbamates inhibits acetylcholine esterase

(AChE), which at the synaptic junctions of cholinergic nerve ending has a crucial role in the hydrolysis of acetylcholine (ACh). These AChE inhibitors excessively stimulate cholinergic receptors by accumulating acetylcholine. Organophosphates and methylcarbamates inhibit AChE through carbamoylation and phosphorylation [40]. About 14 studies for pesticides exposure, 16 for rural residence, 18 for drinking water and 11 for farming has confirmed, that all these factors increases the risk for the development of PD [5-6] Some pesticides are widely and excessively used in the world such as pyrethroids, carbamates and organophosphatase. Most of the pesticides such as, diazinon, malathion, parathion, maneb, pyrethroids, carbamate, paraquat, DDT, organophosphatase and organochlorine induces neurotoxicity and can lead to PD development, that is why UK and other European countries have banned the use of some pesticides while for others they have withdrawn the authorization for manufacturing and utilization [12-13].

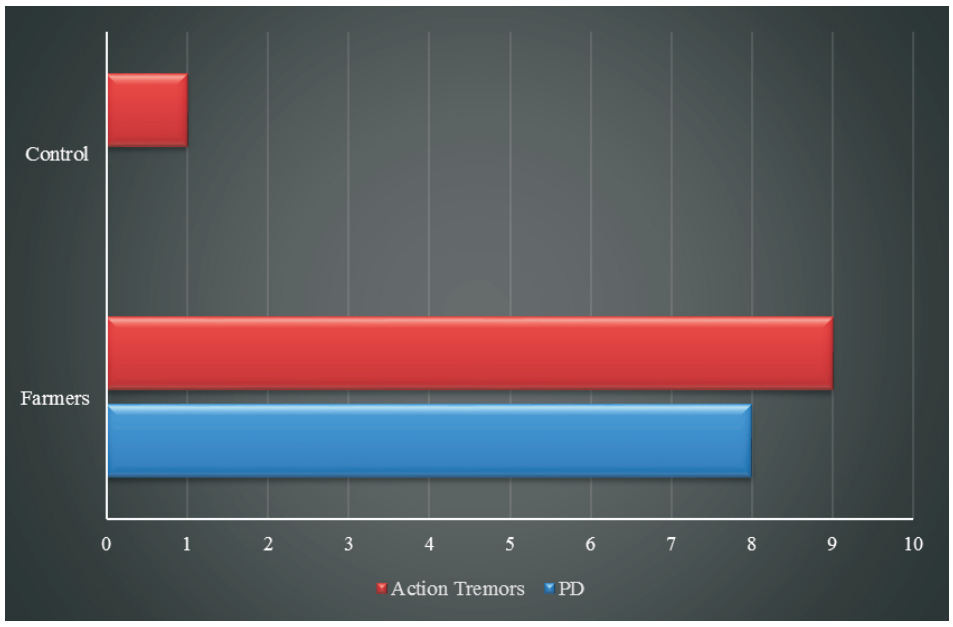


Figure 2: PD and Action Tremors in both the groups

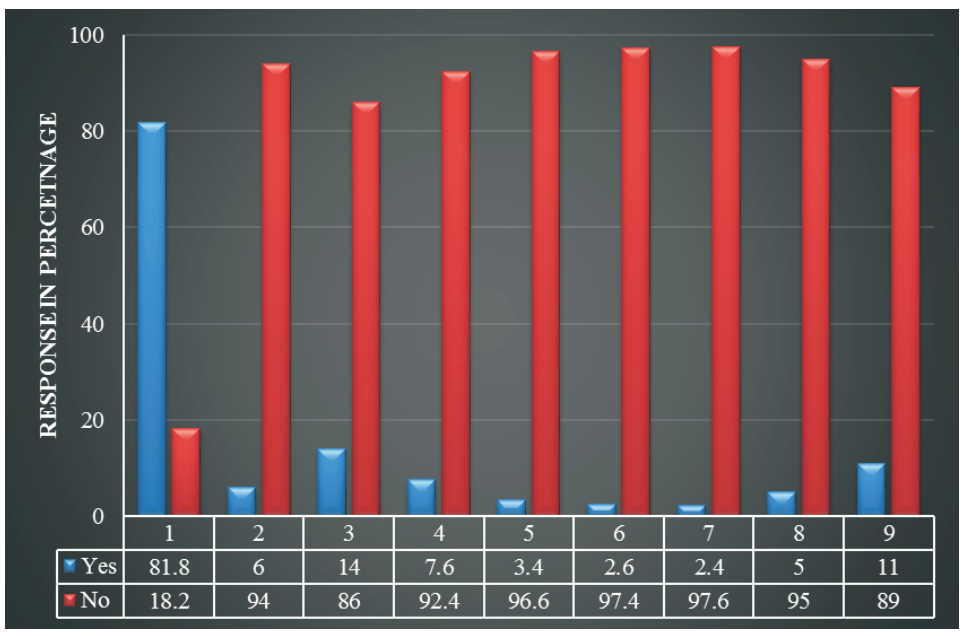
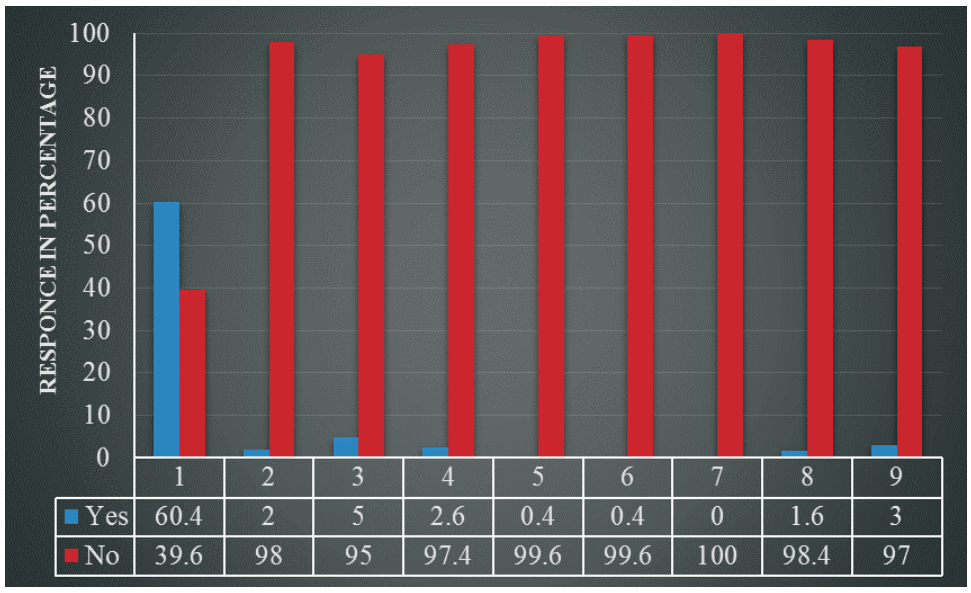


Figure 3: Response of the respondents from Farmers Group (%age)



	1	2	3	4	5	6	7	8	9
Yes	60.4	2	5	2.6	0.4	0.4	0	1.6	3
No	39.6	98	95	97.4	99.6	99.6	100	98.4	97

Figure 4: Response of the respondents from Control Group (%age)

CONCLUSION:

Reckless farmers exposed directly to various pesticides have very serious consequences. One of them is the development of PD. These farmers have very high amount of pesticides in their body as compared to non-exposed and cause neurotoxicity by depleting dopaminergic neurons, leading to progression of PD. In some developing countries banned pesticides are still in use, which seriously affects farmer's health. These reckless farmers are advised to use protective clothing such as dress, mask, gloves etc. during fumigations. They must change their dress and wash their hands with soap. They should be aware about the hazardous effects of pesticides.

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