Neurochemical and Behavioral Dysfunctions in Pesticide Exposed Farm Workers: A Clinical Outcome

Rajesh Kumar Kori¹ · Manish Kumar Singh² · Abhishek Kumar Jain³ ·
Rajesh Singh Yadav¹

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Abstract The problem of pesticides is not new and its exposure to human due to indiscriminate use is largely associated with the health related problems including neurotoxicological alterations. High levels of pesticide residues and their metabolites in the dietary constituents, food materials, maternal blood, cord blood, placenta breast milk have been reported and linked to alterations in birth weight, crown heel length, head circumference, mid-arm circumference and ponderal index of the neonates. Epidemiological studies have suggested that exposure of pesticide to human could be a significant risk factor for neurological disorders, including Parkinson's disease, Alzheimer's disease and multiple sclerosis. Cholinergic and non-cholinergic dysfunctions in pesticide exposed population, especially in children have also been frequently reported in recent years. Developmental neurotoxicity is another concern in the area where pregnant are more prone towards its exposure and which results in the abnormalities in the fetus. In view of the increasing risk of human health through pesticide exposure, the present review has been focused on the studies pertaining to pesticide induced neurochemical alterations and associated behavioral abnormalities in farm workers which could establish a

possible link between the its exposure and associated health hazards.

Keywords Pesticides · Neurotoxicity · Neurobehavior · Suicidal ideation · Farm workers · Neurological disorders

Introduction

The incidences of pesticide poisoning and suicides are very high in developing countries due to poverty, lack of awareness, education and other factors. WHO has reported around 3 million cases of pesticide poisoning with more than 2,50,000 deaths every year world over [1]. Cases of pesticide poisoning from India and many other countries have been frequently reported [1]. In India, most of the population is dependent on traditional agricultural methods, therefore the country is the second largest producer of pesticides in Asia and ranks fourth position in the world for the use of pesticides [2]. However, India, predominantly use insecticide instead of other pesticide (different class of pesticide, i.e. herbicide, weedicide etc.) in contrast to developing countries which enforce higher acute risk of poisoning. The organophosphate pesticide such as monocrotophos and others are expected to involve the highest incidences of suicidal poisoning from different regions and States of India. Recently, Zhang et al. [3] also suggested the association of occupational pesticide poisoning with the decreased neurobehavioral function and enhanced psychiatric morbidity in Chinese farm workers. Pesticides are chemical or mixture of chemical substances widely used to repel unwanted pests including insects, weeds, fungi and rodents which are classified into—insecticide, weedicides, fungicides, rodenticides and fumigants. Insecticides, kill insects by targeting their nervous

✉ Rajesh Singh Yadav
razitrc@gmail.com

¹ Department of Criminology and Forensic Science, School of Applied Sciences, Dr. Harisingh Gour Vishwavidyalaya (A Central University), Sagar, MP 470 003, India

² Department of Biochemistry, Government Medical College, Badaun, UP 243601, India

³ University Health Centre, Dr. Harisingh Gour Vishwavidyalaya (A Central University), Sagar, MP 470 003, India

Fig. 1 Pesticides and their exposure to human beings through agricultural activities, industrial and occupational sources linked with various adverse health effects, altered biochemical and neurotransmitter levels and neurobehavioral outcomes

system, are further divided into organophosphates, pyrethroids, organochlorine and carbamates insecticides. The risk of exposure enhanced many times due to heavy use of pesticides and it could be accidental or occupational during manufacturing, applying, harvesting, handling of crops and public health uses [4]. Human exposure to pesticides is quite imminent due to its indiscriminate and injudicious use in households, agriculture, veterinary practices, occupational and non-occupational settings. Individuals attempting suicides has been frequently reported to take the pesticide intentionally for the purpose [1]. The contamination of food by means of crops routinely sprayed with pesticides is an important source of exposure due to its accumulation in animal's tissue, milk and food products [5]. At the same time high levels of residues of organophosphate, pyrethroids and their metabolites detected in the dietary products and biological tissues of exposed individuals associated with adverse health effects are again a matter of concern. Dewan et al. [6] demonstrated that a significant amount of organophosphates levels in the maternal blood, cord blood, placenta breast milk alters several parameters like birth weight, crown heel length, head circumference, mid-arm circumference and ponderal index of the neonates. The metabolites of pyrethroid have been detected in the urine of pregnant women and children of preschool [7]. The toxic effects of pesticides could be determined by the dose, route, time of exposure, and rate of metabolism. Some long-term health impacts are delayed or not immediately apparent, such as infertility, birth defects, endocrine disruption, neurological disorders and cancer [8]. Incidences of both acute and chronic exposure have been found in farm workers during agricultural activities including spraying, mixing, loading of pesticides. The exposure pattern become quite high due to unawareness of toxic effects of pesticides and no use of suitable protective equipment during the pesticide application.

Several epidemiological studies have identified pesticide exposure as a significant risk factor for neurological disorders, including Parkinson's disease, Alzheimer's disease and multiple sclerosis [2, 9]. The other negative outcome of pesticide exposure includes birth defects, fetal death, still, pre-term birth, adverse pregnancy outcomes and neurodevelopmental disorder [10, 11]. Association of pesticide exposure with the incidence of chronic diseases, genetic damages, epigenetic modifications, endocrine disruption, mitochondrial dysfunction, oxidative stress, impairment of the ubiquitin proteasome system and defective autophagy has also been frequently reported [12]. Developing fetus and children are at high risk of exposure and allied adverse consequences due to immature blood brain barrier and detoxification mechanism. In the real life situation the use of mixtures of pesticides is commonly observed and it is also related to higher incidence of pesticide poisonings and deaths [13]. The present review has therefore been focused on pesticide induced neurochemical alterations and associated behavioral abnormalities in farm workers to establish a possible link between the pesticide exposure and behavioral change in human with possible clinical implications (Fig. 1).

Biochemical Modifications and Adverse Clinical Outcomes

Occupational exposure to pesticides resulted in alterations of some hematological parameters including decrease size of red blood cells, higher platelet and WBC counts (increase in lymphocyte and monocyte count) [14, 15]. Increased activities of GGT, ALP bilirubin has also been shown to be linked to the hepatic cell damage in pesticide exposed condition [14]. Elevated levels of plasma urea and creatinine suggested nephrotoxic changes in workers

occupationally exposed to pesticides have also been reported [16]. Studies have been demonstrated that the long term exposure of pesticides in individuals may lead to the development of vascular diseases, decrease in the activity of butylcholinesterase and acetylcholinesterase and alterations in hematological parameters [14, 17, 18]. Organophosphate induced biochemical alteration associated with the adverse health effects, including dizziness, headache and anxiety has been reported in the farm workers [19, 20]. Impaired motor coordination, reduced motor conduction velocity, verbal memory and other neurological and neuropsychiatric effects has been shown in farm workers [21–23]. The detailed symptomatic effects followed by organophosphate exposure have been represented in the Table 1 [24–34]. Besides organophosphates, organochlorine and pyrethroids has also been frequently used in the agriculture and found to be linked with the adverse neurological consequences. Autism spectrum disorders in the children of female farm workers and risk of Alzheimer's disease and genetic disorders have been reported in Table 2 [35–43]. Limited studies have been published which suggested the multiple pesticide exposure at a time in humans than that of single toxicant. Mixtures of organophosphates, carbamates and pyrethroids has reported to cause synergistic effects and is a matter of great concern. It has been shown to cause depression, anxiety, obsessive compulsiveness and other central nervous system problems as given in Table 3 [44–49]. Synergistic interaction can also be expected in mixtures of pesticides, as or may act on totally different systems and thus not interact. Furthermore, even a single chemical may have multiple effects and affect more than one organ system. Effects may vary with age and metabolites may have totally different actions from the parent compound. In a study on French general population, Crepet et al. [50] conducted a research through PERICLES research program to assess the potential combined effects of pesticide mixtures. They suggested that in pesticide mixtures exposed population, the toxic effects cannot be predicted based on the toxic potential of each compound as observed in human cells.

The role of oxidative stress in pesticide induced neurotoxicity has been well established and associated with various neurological disorders including Alzheimer's and Parkinson's diseases. Exposure to pesticide in humans is mainly associated with enhanced generation of free radical species which caused an increased level of lipid peroxidation and decrease antioxidant capacity, including reduced glutathione, superoxide dismutase, catalase and subsequently turns into the diseased conditions [51, 52]. These free radicals act on the mitochondria to trigger the apoptotic cascade and involves in the process of neurodegeneration. Further, the oxidative damages cause alterations in the mitochondria permeability transition and

disrupts calcium homeostasis, leading to apoptosis and cell death. Due to lipophilic nature, pyrethroids and other class of pesticides accumulate in biological membranes and tissues leading to oxidative insult. The toxic products produced as a result of oxidative stress including malondialdehyde, 4-hydroxynonenal (HNE) and acrolein have been found to disturb the homeostasis of cell in the body and alter the cellular structure and physiological functions [53].

Neurochemical Alterations and Behavioral Abnormalities

Several pesticides such as endosulfan, acephate, chlorpyrifos, dichlorvos and methamidophos are found to be involved in the endocrine disruption and reproductive toxicity hence, cause adverse health effects on the human and fetus [54]. Leon-Olea et al. [55] demonstrated that behavioral features affected by some of pesticide include cognitive deficits, heightened anxiety or anxiety-like, socio-sexual, locomotor and appetitive behaviors. The inhibition of AChE and BChE activities in the pesticide exposed group has been frequently reported [14, 56]. Therefore, the cholinesterases activities could be useful biomarkers in the monitoring of populations exposed to pesticides [57]. Pyrethroids have been found to alter the levels of neurotransmitters and metabolites of monoamine neurotransmitters in the brain. Organophosphate pesticides inhibited the enzyme AChE leading to the production of an excessive amount of ROS, which is due to the inhibition of oxidative phosphorylation [58]. Srivastava et al. [59] showed that workers exposed to quinalphos, an organophosphate pesticide had altered plantar and ankle reflexes and also learning and memory impairment. A range of cognitive, psychomotor and emotional behavior, including impaired memory, attention, alertness, depression, anxiety and irritability impairments have also been reported to result from chronic and low level organophosphorus exposure studies [60]. The relevance of a serotonin and dopamine model of aggression in the major risk factor for suicide has been demonstrated [61]. Also, the role of serotonin and dopamine in depressed mood and possibly the individual's ability to cope with imminent suicidality have been suggested [62]. The serotonergic system have rejuvenated its role in depression and identified additional associations with suicidal behavior, impulsive aggression, eating disorders, obsessive-compulsive disorder and anxiety [62]. Exposure of pyrethroids and other insecticide to human could decrease brain serotonin levels [63] which may be linked to the decreased synthesis of serotonin and loss of serotonergic neurons. Chronic exposure to pyrethroids and other group of pesticides have

Table 1 Chronic exposure of organophosphate to farm workers and its association with the exposure pattern, adverse health effects, neurochemical and behavioral dysfunctions

Type of pesticide and place	Subject (N)	Types of exposure	Common health effects	Neurochemical and behavioral alterations	References
Organophosphates (OPs)	Farm workers (N = 247)	Occupational exposure	Dizziness and headache	Dizziness, sleepiness and headache had a significantly higher overall neurological symptom score ($p < 0.05$)	London et al. [19]
South Africa					
OPs	Farm workers (N = 44)	Occupational and residential exposure	Anxiety	Anxiety score of the pesticide applicators was significantly higher ($p < 0.05$) than that of the farmers.	Levin et al. [20]
USA					
OPs	Farm workers (N = 24)	Occupational exposure	Headache (59%), giddiness (50%), ocular symptoms (27%) and Paraesthesia (18%)	Reduced motor conduction velocity and serum AChE levels	Misra et al. [21]
India					
OPs	Pesticide applicators (N = 701)	Occupational and residential exposure	Not examined	Reduce in the verbal memory, motor speed and motor coordination	Starks et al. [22]
(Iowa and North Carolina)					
OPs	Farm workers (N = 57)	Occupational and residential exposure	Not examined	Some neurological and neuropsychiatric effects on adults like ADHD, anxiety, depression disorder	London et al. [23]
(W. Cape province of SA)					
OPs	Pesticide applicators (N = 216)	Occupational exposure	Muscle pain in the lower limbs, distal numbness and paraesthesiae occur, followed by progressive weakness, depression of deep tendon reflexes in the lower limb	Organophosphate-induced delayed polynuropathy	Lotti and Moretto [24]
Italy					
OPs	Pesticide applicators (N = 66)	Occupational exposure	Not examined	Worse performance in neuropsychological functions attention, reasoning, memory, perception, visuomotor skills, expressive language and motor performance	Roldan-Tapia et al. [25]
Southeastern Spain					
OPs	Farm workers (N = 37)	Occupational and residential exposure	Dermatitis, diarrhea, abdominal pain, and sialorrhea	Headache, hypertension, anxiety and depression disorders higher in exposed population than controls	Salvi et al. [26]
southern Brazil					
OPs	Pesticide applicators as well as suicide attempters (N = 1838)	Occupational as well as accidental exposure	Acute and chronic OP exposure is associated with affective disorders	Suicide rates are high in farming populations.	London et al. [27]
Asia, Africa, America					
OPs	Agricultural workers (N = 119)	Occupational exposure	Not examined	Neurological impairment as measured by the attention, remembrance, reaction time and deficits in neurobehavioral performance	Rohlman et al. [28]
(Oregon, USA)					
OPs	Farm workers (N = 479)	Occupational and residential exposure	Eye irritation, nausea or vomiting, skin irritation	High depressive symptoms, and headache dizziness	Stallones and Beseler [29]
(Northeastern Colorado)					

Table 1 continued

Type of pesticide and place	Subject (N)	Types of exposure	Common health effects	Neurochemical and behavioral alterations	References
OPs (London)	Farm workers (N = 37)	Occupational and residential exposure	Not examined	Slower response on neuropsychological performance like processing speed, attention	Stephens and Sreenivasan [30]
OPs (London, UK)	Sheep dipping farmers (N = 612)	Occupational and residential exposure	Not examined	Sensory and vibration thresholds were higher, neurological symptoms	Pilkington et al. [31]
OPs (Egypt)	Farm workers (N = 52)	Occupational and residential exposure	Not examined	Serum acetylcholinesterase was significantly lower, neurological abnormalities	Farahat et al. [32]
OPs Oregon and Columbia, USA	Farm worker (N = 46)	Occupational and residential exposure	Not examined	Lower neurobehavioral performance like learning test, symbol-digit, reaction time	Rothlein et al. [33]
OPs N. and S. West regions of England	Farm workers (N = 127)	Occupational and residential exposure	Not examined	Significantly higher anxiety and depression in exposed population	Mackenzie Rossa et al. [34]

been found to involve multiple sites within the central nervous system, leading to neurobehavioral and neurochemical alterations.

The postmortem studies to find out the role of dopamine and serotonin in aggressive behavior and development of suicidal tendency in human have been carried out, but have variable results due to differences in age, presence of psychotropic medications and also have unique pathobiology [64]. Altered levels of homovanillic acid (HVA) have been found in the frontal cortex and basal ganglia of suicide victims [65]. Concentration of HVA in cerebro-spinal fluid has been found to be lower in suicide attempters than controls [66]. Behavioral and functional changes have been found to be associated with the alterations in dopaminergic system that further linked with delayed neurotoxicity [67]. Pesticide poisoning is found to be one of the risk factors for depression, which, if addressed timely, may reduce risk of suicides among agriculture workers [68, 69]. The studies have been reported that specific depressive symptoms occur more often in those with a pesticide poisoning and these symptoms lead to an increased risk of farm injuries [45, 70]. Studies have been carried out to explore possible causal pathways between pesticide exposure and depression, impulsivity, suicide ideation and eventual suicide [71]. Saravi and Dehpour [72] suggested the correlation of environmental as well as genetic factors to the pathophysiology of neurodevelopmental and neurobehavioral defects. They further demonstrated that maternal exposure to organochlorine pesticides results in impaired motor and cognitive development in newborns and infants. Also, occupational exposure to the pesticides in farmers and chemical workers leads to brain damage, cognitive deficits, behavioral and neurodegenerative disorders.

Molecular Targets and Mechanism of Action

Inhibition of cholinesterase activity in case of organophosphates, carbamates and prolonged opening of voltage sensitive sodium channels in case of pyrethroids and organochlorine have been identified as the most common causes of severe acute pesticide poisonings [73]. The primary mechanism of organophosphate toxicity is the inhibition of AChE in the nervous system and the resultant over activation of cholinergic tone via acetylcholine accumulation in synapses and neuromuscular junctions [74]. Pesticide exposure also found to be associated with the mitochondrial dysfunction and cell death through the initiation of apoptotic pathways [73]. Dysfunction in the mitochondrial complexes I and IV due to disruption in oxidative phosphorylation have been reported following exposure to pesticides [75]. Assessment of pesticide

Table 2 Chronic exposure of organochlorine and pyrethroid to farm workers and their association with the exposure pattern, adverse health effects, neurochemical and behavioral dysfunctions

Type of pesticide and place	Subject (N)	Types of exposure	Common health effects	Neurochemical and behavioral alterations	References
Organochlorine (OC) (p,p'-DDE) Finland	Females farmworkers (N = 150)	Occupational and residential exposure	Maternal serum sample prior pregnancy	Autism spectrum disorders (ASD), neurodevelopmental disorders	Cheslack-Postava et al. [35] and Roberts et al. [36]
OC (Texas)	Farm residents (N = 165)	Occupational and residential exposure	Not examined	Exposure of human neuroblastoma cells to DDT or DDE increased levels of amyloid precursor proteins, Alzheimer's disease	Richardson et al. [37]
OC (Dieldrin, DDT, PCBs, HCB)	Farm workers (N = 145)	Occupational and residential exposure	Not examined	Risk of Alzheimer's disease (AD) in the north Indian population AD	Singh et al. [38] and Kim et al. [39]
OC Mexico Community	Farm Workers (N = 41)	Occupational and residential exposure	Acute poisoning (20% of the cases) and diverse alterations of the digestive, neurological, respiratory, circulatory, dermatological, renal, and reproductive system	Free DNA fragments in plasma (90.8 vs 49.05 ng/mL) as well as a higher level of lipid peroxidation	Payan-Rentería et al. [40]
OC (DDT and DDE) USA	Mexican farm-workers (N = 360)	Occupational and residential exposure	Not examined	No association with mental development at 6 months but a 2- to 3-point decrease in Mental Developmental Index scores for p,p'-DDT and o,p'-DDT at 12 and 24 months, corresponding to 7- to 10-point decreases across the exposure range	Eskenazi et al. [41]
PYR Philippines	Farmers (N = 542)	Occupational and residential exposure	Alteration in haematological parameters	Abnormal cranial nerve function, and motor strength	Lu et al. [42]
PYR Bolivian	Farm sprayers (N = 120)	Occupational exposure	Not examined	Deterioration in neurocognitive performance	Hansen et al. [43]

Table 3 Chronic exposure of mixture of pesticides (Organophosphate, carbamate, organochlorine and pyrethroid) to farm workers and their association with the exposure pattern, adverse health effects, neurochemical and behavioral dysfunctions

Type of pesticide and place	Subject (N)	Types of exposure	Common health effects	Neurochemical and behavioral alterations	References
OPs and Carbamates, PYR China	Farm workers (N = 121)	Occupational and residential exposure	Not examined	Higher anger-hostility, depression-dejection, tension-anxiety and lower for vigor-activity compared to controls	Zhang et al. [3]
OPs and Carbamates Sri Lanka	Farmers (N = 260)	Occupational and residential exposure	Not examined	More inhibition of cholinesterase activity in exposed population	Smit et al. [44]
OPs and Carbamates	Banana farm workers (N = 78)	Occupational and residential exposure	Not examined	Somatization, obsessive-compulsiveness, interpersonal sensitivity, depression and anxiety	Wesseling et al. [45]
OPs and Carbamates Kenya, East African	Pesticide applicators (N = 256)	Occupational and residential exposure	Respiratory, eye disorders	Inhibition of cholinesterase activity and central nervous system problems	Ohayo-Mitoko et al. [46]
OP and OCs (Iowa and North Carolina)	Pesticides used by applicators (N = 21,208)	Occupational and residential exposure	Not examined	Positive association between pesticide exposure and depression	Beard et al. [47]
OPs and others Northeastern Colorado, USA	Agricultural workers and spouse (N = 684)	Occupational and residential exposure	Not examined	Poor health, financial difficulties and a history of pesticide poisoning significantly explained the depressive symptoms	Beseler et al. [48]
PYR and Ops Western Cape South Africa	Farm workers (n = 121)	Occupational and residential exposure	Not examined	Problems with buttoning, reading and notes	Motsoeneng and Dalvie [49]

induced toxicity and its interaction with the body could be done by analysis between the genetic polymorphisms studied (PON1192, PON155, PON1-108, PON1-909, GSTM1, GSTT1, BCHE), cholinesterase activities (AChE and BChE) and erythrocyte enzyme levels, only a few studies have addressed gene–environment interactions in populations exposed to pesticides [76]. In addition to this, a number of signaling cascade has been found to be involved in the neurotoxicity of pesticides. Decreased expression of Bcl2 and increased expression of Bax, Caspases-3, 9, JNK1, 2, TrkA/p75 have been reported in pesticide exposed individuals [77, 78]. Although a number of epidemiological studies have been carried out on pesticide exposed farm workers, but the exact mechanism of toxicity in human is still not fully understand. For this, various experimental studies were performed by health scientist to explore the pathways involved in the neurobehavioral toxicity and could be a possible tool for the preventive approach. Studies have been demonstrated that low level repeated exposure of organophosphates in cultured neural cells induces inflammatory responses, which could be linked with the impaired learning and memory [79]. Liu et al. [80] suggested that exposure to PCB153 and p,p'-DDE in rats and human thyroid follicular epithelial cell lines activated the PI3 K/Akt and MAPK pathways which finally disrupt the hypothalamic-pituitary-thyroid (HPT) axis via TR β 1 and TRHr and then decrease TH levels and hence disturb TH homeostasis.

Conclusions

Exposure to pesticides in humans has been found to alter the biochemical levels and influence the hematological profile, liver and kidney functions and lipid profile which could be used as suitable biomarkers for the development of therapeutic approaches. Cholinergic and non-cholinergic systems linked to depression, impulsivity and mood disturbances has also found to be affected following pesticide exposure in humans, which could explain an elevated association of pesticide exposure with suicidal ideation and other behavioral alterations. The modulation in serotonergic and dopaminergic transmission affects the emotional state of a person and aggravate aggression which might lead to fatal consequences. The use of pesticides and its associated neurochemical alterations leading to behavioral deficits in both children and adults become a serious concern among the health scientists. There is a strong need of translational research to understand the detailed mechanism of neurobehavioral toxicity in individuals chronically exposed to pesticides. The present review may help to understand the detailed mechanism of pesticide induce behavioral changes and to find out preventive measures

accordingly. The study may provide new insights into neurobehavioral toxicity and open new vistas for regulatory agencies to draw suitable guide maps for its use, risk assessments and reviews the threshold limit values.

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Compliance with Ethical Standards

Conflict of interest Authors declares no conflict of interest.

Ethical Approval This is a review article and does not contain any studies with human participants or animals performed by any of the authors.

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