THE RELATIONSHIP BETWEEN RESPIRATORY HEALTH AND SERUM LEVEL OF BRAIN-DERIVED NEUROTROPHIC FACTOR AMONG PESTICIDE WORKERS

By

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Abstract

Introduction: Workers who handle organophosphorus (OP) pesticides have a serious risk of developing respiratory disorders. Neurotrophins, including brain-derived neurotrophic factor (BDNF), play a crucial role in obstructive airway diseases. **Aim of Work:** To investigate whether OP pesticide exposure affects the respiratory system through the evaluation of respiratory symptoms, ventilatory function tests, and blood concentrations of brain-derived neutrophilic factor (BDNF). **Materials and Methods:** Forty-five male workers exposed to OP pesticides from a pesticide facility were compared to 45 male administrative employees (control group). Both groups underwent comprehensive assessments, including history, clinical examination, spirometry, and serum BDNF measurements. **Results:** The exposed workers exhibited a higher incidence of respiratory symptoms and obstructive pattern impairment of ventilatory functions and an increase in serum BDNF levels compared to the non-exposed personnel. Moreover, a negative correlation was identified between obstructive ventilatory function parameters and serum BDNF levels in the exposed group, whereas a positive association was observed between age and smoking index and serum BDNF levels. **Conclusion and Recommendations:** Workers who are exposed to OP pesticides may have a higher risk of respiratory disorders and higher blood levels of BDNF. It is recommended that workers in agricultural and related industries should take appropriate measures to minimize exposure.

Keywords: Organophosphorus, Pesticide workers, Respiratory disorders, Ventilatory function, Brain-derived neurotrophic factor (BDNF) .

Introduction

Pesticides, which are chemicals utilized to control unwanted pests, pose health risks to both workers and the public. Those commonly exposed include farmworkers, gardeners, and production staff. High exposure occurs during pesticide production, and application, with adverse effects on health (Kim et al., 2017). Workplace exposure to pesticides occurs during various stages, including production, delivery, application, and equipment cleaning (Kalyabina et al., 2021). Entry into the body primarily happens through the skin, respiratory system, and digestive system, particularly during activities like fumigation and mixing (Tudi et al., 2021).

Pesticide exposure can lead to acute symptoms such as vomiting, diarrhea, convulsions and headaches (Mamta et al., 2023). Prolonged exposure is correlated to thyroid disease, obesity, skin disorders, respiratory illnesses, and neurological impairments (Saleh et al., 2020; Sudjaroen et al., 2020).

Persistent respiratory disorders, including asthma, chronic obstructive pulmonary disease (COPD), pulmonary tumors, and reduced pulmonary capacities may be related to exposure to pesticides, according to previous study (Tarmure et al., 2020). Furthermore, chronic bronchitis, respiratory muscle dysfunction, and lung hyperinflation have all been linked to worker exposure to organophosphorus (OP) pesticides, according to study by Nurcandra and colleagues (2020).

Neurotrophins, including brain-derived neurotrophic factor (BDNF), play a crucial role in obstructive airway diseases (Freeman et al., 2017). Elevated levels of BDNF have been correlated with a decline of pulmonary function parameters in patients with allergic asthma. BDNF is essential in both acute and long-term inflammatory disorders of the airways, inducing airway smooth muscle cell proliferation and triggering neuronal hyperactivity, resulting in coughing and enhanced airway responsiveness (Aravamudan et al., 2012). OPs impact various factors involved in neural plasticity regulation, potentially altering neurotrophin expression in the brain, as suggested by preclinical models of chronic low-dose OP exposure (Betancourt et al., 2007; Lee et al., 2016). Given that upon inhalation, all chemicals are directed towards the lung, it is reasonable to expect impairment in lung functions following pesticide inhalation exposure

Aim of Work

To investigate whether OP pesticide exposure affects the respiratory system through the evaluation of respiratory symptoms, ventilatory function tests, and blood concentrations of brain-derived neutrophilic factor (BDNF).

Materials and Methods

Study design: A cross-sectional analytical study

Place and duration of the study: This study was conducted from November 2023 to February 2024 at an OP pesticide facility in Egypt.

Study sample The study involved forty-five randomly selected male workers directly exposed to OP substances, and 45 administrative workers served as a control group randomly selected from administrative staff with no prior workplace exposure to pesticides or other chemical agents.

Chlorpyrifos, profenofos, and malathion were the main OPs manufactured in the study facility. There were two types of employees in the factory: applicators, who loaded backpack sprayers, applied pesticides, and maintained cleanup supplies, and formulators, who produced and formulated OPs compounds. All workers in the study facility were men and worked in different environments, some of which were open or partially enclosed. The research facility's architecture included systems for automatically eliminating gases and particles. Additionally, the roof's apex openings and periodically open doors help to provide the workplace with natural ventilation. Most personnel who were exposed to pesticides utilized personal protective equipment (PPE) such as respirators with specific masks and gloves.

Inclusion criteria of the studied sample: Workers who provided informed consent to partake in the research and with a minimum of one year of employment tenure. **Exclusion criteria**: Acute infections or exacerbations of COPD that have occurred within the previous four weeks, Clopidogrel use (an antiplatelet agent used to prevent intravascular blood clots; the exclusion of individuals taking clopidogrel was based on its impact on BDNF serum levels, unlike aspirin treatment, which does not influence BDNF levels), presence of any malignant disorder.

Sample size

Sample size calculation was done using the comparison of FEV1/FVC as an indicator of airway obstruction between individuals exposed to organophosphorus pesticides and non-exposed matched individuals. As reported in previous publication (Fareed et al., 2013), the mean ± SD of FEV1/FVC in exposed group was 0.79 ± 0.01, while in non-exposed group it was 0.84 ± 0.01. Accordingly, we calculated that the minimum proper sample size was 45 participants in each group to be able to detect a real difference in FEV1/FVC of 0.006 with 80% power at $\alpha = 0.05$ level using Student's t test for independent samples. Sample size calculation was done using PS Power and Sample Size Calculations Software, version 3.1.2 for MS Windows (William D. Dupont and Walton D., Vanderbilt University, Nashville, Tennessee, USA).

Study methods

1- Self structured questionnaire:

Comprehensive medical histories were obtained from all employees, with particular attention to personal and occupational exposures, as well as family history. The American Thoracic Society's (ATS) respiratory symptoms questionnaire was used to investigate the prevalence of respiratory symptoms, such as wheezing, cough (either productive or not) and dyspnea.

2- **Clinical examination** focusing on the respiratory system was conducted for each participant. Furthermore, the formula for the smoking index was (years of smoking × number of cigarettes smoked/day (CPD)). The individuals' Body Mass Index (BMI) was computed by dividing their weight in kilograms by the area of their height in square meters, using their height and weight as input.

3- Laboratory investigations:

Serum BDNF level:

In an aseptic environment, a vein puncture was conducted using a disposable plastic syringe to withdraw 3 mL of venous blood from each participant around 8 a.m., approximately 12 hours after their last meal. The blood, collected without anticoagulants, was transferred into sterile tubes. After coagulation, serum separation was achieved by centrifugation at 2000xg at room temperature. The serum was stored at -20°C until BDNF concentration quantification could be performed.

The enzyme-linked immunosorbent

assay (ELISA) was used to measure the serum BDNF levels in accordance with the manufacturer's instructions, RayBio® Human BDNF ELISA Kit (Catalog Number: ELH-BDNF). BDNF concentrations were reported in ng/mL for serum samples.

4- Ventilatory function tests:

Ventilatory function tests were conducted using a portable spirometer "Flow Handy ZAN 100 USB Pulmonary Spirometer following ATS/ERS recommendations. Parameters assessed included FEF (forced expiratory flow), FEV1 (forced expiratory volume in the first second), FVC (forced vital capacity), and FEV1/FVC ratio. FVC values below 80% and FEV1/FVC values below 70% indicate restrictive and obstructive patterns, respectively (Neder, 2022).

Consent

Written informed consents were signed by all participants before being enrolled in the study.

Ethical Approval

The study was approved by the Ethical Committee of the Faculty of Medicine, Cairo University in Egypt, (N-466-2023) and was conducted following the ethical guidelines of the Declaration of Helsinki October 2013. Approval from the chief executive officer of the pesticide factory was also obtained.

Data Management

Input and coding of the data were performed using version 28 of the Statistical Package for the Social Sciences (SPSS) (IBM Corp., Armonk, NY, USA). The means, standard deviations, medians, minimums, and maximums were employed to summarize the quantitative variables. Frequencies (number of cases) and relative frequencies (calculated as percentages) were employed to represent categorical information.

Comparisons between groups were done using un-paired t-test or analysis of variance (ANOVA) with multiple comparisons post hoc test in normally distributed quantitative variables while non-parametric Mann-Whitney test was used for non-normally distributed quantitative variables. For comparing categorical data, Chi square ($\chi 2$) test was performed. Fisher exact test was used instead when the expected frequency is less than 5.Correlations between quantitative variables were done using Spearman correlation coefficient. Linear regression analysis was done to detect independent predictors of BDNF. A P-value of less than 0.05 met the statistical significance threshold.

Results

The study involved 90 participants divided into two groups: 45 male factory workers producing OP pesticides in Egypt, and 45 administrative workers not exposed to pesticides at work. Subjects were matched based on BMI, smoking status, age, and gender, with no statistically significant differences observed between pesticide-exposed and unexposed group regarding these variables.

Pesticide-exposed workers had a work duration ranging from 1 to 35 years, with a mean of 18.76 years. They were exposed to OP pesticides for 6 to 8 hours per day, at least 5 days a week. Among them, 77.8% were involved in formulating pesticides, while 22.2% were applicators (non tabulated results).

Table 1: Distribution of the studied groups based on general characteristics, respiratory complaints, and ventilatory test results.

Count		**Pesticide exposed workers**		**Unexposed group**		**P-value**
		%	**Count**	**%**	**Count**	
Smoking	**Yes**	23	51.1%	18	40.0%	0.290
Cough	**Yes**	22	48.9%	3	6.7%	**< 0.001***
Expectoration	**Yes**	19	42.2%	3	6.7%	**< 0.001***
Chest pain	**Yes**	6	13.3%	1	2.2%	0.110
Wheezes	**Yes**	16	35.6%	1	2.2%	**< 0.001***
Chest tightness	**Yes**	10	22.2%	2	4.4%	**0.013***
Nasal irritation	**Yes**	6	13.3%	0	0.0%	**0.026***
Dyspnea	**Yes**	20	44.4%	3	6.7%	**< 0.001***

Ventilatory functions	**Normal ventilatory functions**	34	75.6%	44	97.8%	**0.003***
	Restriction (FVC<80)	2	4.4%	1	2.2%	
	Obstruction (FEV1/ FVC<70)	7	15.6%	0	0.0%	
	Combined	2	4.4%	0	0.0%	

FVC: forced vital capacity, FEV1: forced expiratory volume in the first second.

*: Statistically significant P < 0.05.

Table 1 showed statistically significant difference among exposed group regarding respiratory manifestations including cough, expectorations, wheezes, chest tightness, dyspnea and nasal irritation compared to the unexposed group.It also showed that there was a statistically significant difference between the studied groups as regards obstructive patterns as it was higher among the exposed group. However, restrictive impairment was higher among the exposed group compared to the control but with no statistically significant difference.

Table 2: Mean ± standard deviation of age, smoking index, duration of employment, ventilatory function parameters, and serum level of BDNF among the studied participants

	Pesticide exposed workers				**Unexposed group**				**P-value**
	Mean	**SD**	**Median**	**Minimum-Maximum**	**Mean**	**SD**	**Median**	**Minimum-Maximum**	
Age	40.78	8.85	42.00	24-55	41.18	8.30	41.00	28-59	0.825
Duration of work (years)	18.76	9.11	19.00	5-35	15.44	9.48	12.00	2-37	0.095
BMI (Kg/m^2)	28.30	5.36	28.20	18.3-42.9	28.92	3.75	29.20	20.9-36.3	0.528
FVC %	97.33	14.43	96.00	64-132	101.18	14.32	103.00	64-131	0.208
FEV1 %	89.53	15.65	91.00	49-115	103.36	15.04	102.00	78-137	**< 0.001***

FEV1/FVC %	76.27	7.96	78.00	54-87	84.76	4.96	86.00	72-100	**< 0.001***
PEF %	70.29	20.98	69.00	37-131	82.36	17.41	86.00	38-107	**0.004***
MEF 75 %	71.58	22.28	70.00	31-115	90.58	20.77	96.00	27-118	**< 0.001***
MEF 50 %	74.18	26.33	76.00	19-128	107.69	32.60	103.00	29-180	**< 0.001***
MEF 25 %	66.27	26.10	66.00	15-115	100.71	32.59	99.00	48-191	**< 0.001***
Serum BDNF (ng/mL)	203.60	62.56	201.20	110.2-299.7	171.34	45.54	176.10	110-283.7	**0.006***

BMI: Body Mass Index, FVC: forced vital capacity, FEV1: forced expiratory volume in the first second, PEF: peak expiratory flow, MEF: Maximum expiratory flow, BDNF: Brain-derived neurotrophic factor. * : Statistically significant p < 0.05.

Table 2 showed statistically significant differences between the two studied groups in terms of higher mean serum BDNF levels and lower mean FEV1%, FEV1/FVC, PEF%, MEF25%, MEF50%, and MEF75% among pesticide-exposed workers.

Table 3: Relationship between serum BDNF levels and personal characteristics, respiratory symptoms, and ventilatory function test results among pesticide-exposed workers

		Serum BDNF (ng/mL)				**P-value**
Mean		**SD**	**Median**	**Minimum-Maximum**		
Current occupation	**Formulators**	195.05	64.55	190.50	110.2-299.7	0.086
	Applicators	233.53	45.98	227.65	176.5-298.1	
Cough	**Yes**	200.74	65.72	206.85	113.4-296.1	0.768
	NO	206.34	60.74	197.80	110.2-299.7	

Expectoration	**Yes**	200.21	64.43	212.50	113.4-296.1	0.759
	NO	206.08	62.33	199.50	110.2-299.7	
Chest pain	**Yes**	211.60	82.47	229.85	110.2-296.1	0.741
	NO	202.37	60.21	197.80	110.9-299.7	
Wheezes	**Yes**	223.03	57.48	217.35	125.1-296.1	0.123
	NO	192.88	63.61	190.50	110.2-299.7	
Chest tightness	**Yes**	211.75	68.45	214.30	110.2-296.1	0.646
	NO	201.27	61.64	197.80	110.9-299.7	
Nasal irritation	**Yes**	192.52	86.04	170.60	113.4-294.8	0.646
	NO	205.31	59.46	201.20	110.2-299.7	
Dyspnea	**Yes**	217.75	59.51	217.35	113.4-298.1	0.178
	NO	192.28	63.81	182.50	110.2-299.7	
Finding in ventilatory function	**Normal ventilatory functions**	179.22	49.50	179.45	110.2-278.3	**< 0.001***
	Restriction (FVC<80)	221.80	3.25	221.80	219.5-224.1	
	Obstruction (FEV1/ FVC<70)	289.66	9.55	294.80	276.3-299.7	
	Combined	298.65	0.78	298.65	298.1-299.2	

FVC: forced vital capacity, FEV1: forced expiratory volume in the first second, BDNF: Brain-derived neurotrophic factor * :Statistically significant $p < 0.05$.

Table 3 showed that the mean of serum BDNF levels were higher among pesticide applicators compared to formulators, with no statistically significant differences (233.53 ± 45.98 vs. 195.05 ± 64.55, respectively), while there were no statistically significant difference regarding serum BDNF and any of the respiratory manifestations. There was a statistically significant increased serum BDNF among workers with ventilatory function abnormalities where workers with obstructive ventilatory dysfunction exhibited significantly higher levels of serum BDNF, however those having combined (obstruction and restriction) had the highest mean serum level.

Table 4: Spearman correlation coefficients between serum level of BDNF and age, smoking index, duration of work, and ventilatory function parameters in pesticide-exposed workers

	Serum BDNF (ng/mL)	
	Correlation coefficient	**P-value**
Age	0.310	**0.038***
Smoking index (CPD× years of smoking)	0.351	**0.018***
Duration of work (years)	0.238	0.115
BMI (Kg/m2)	0.078	0.610
FVC %	-0.198	0.192
FEV1 %	-0.349	**0.019***
FEV1/FVC %	-0.536	**< 0.001***
PEF %	-0.254	0.093
MEF 75 %	-0.242	0.109
MEF 50 %	-0.450	**0.002***
MEF 25 %	-0.439	**0.003***

BMI: Body mass index, FVC: Forced vital capacity, FEV1: Forced expiratory volume in the first second, PEF: peak expiratory flow, MEF: Maximum expiratory flow,

BDNF: Brain-derived neurotrophic factor *: Statistically significant $p < 0.05$.

Table 4 showed a statistically significant positive relationship among pesticide-exposed workers between serum BDNF levels, age, and smoking index. Furthermore, within the exposed group, a statistically significant inverse association was identified between serum BDNF levels and parameters of ventilatory functions (FEV1%, FEV1/FVC, MEF50%, and MEF25%) and serum BDNF concentration.

Table 5: Multivariate linear regression analysis to detect independent predictors of BDNF in pesticide-exposed workers.

Model B		Unstandardized coefficients		Standardized coefficients	t	P-value Lower bound	95.0% Confidence interval for B	
		Std. Error	**Beta**				**Upper bound**	
Serum BDNF (ng/mL)	**(Constant)**	568.928	72.794		7.816	**<0.001***	422.125	715.730
	FEV1/FVC %	-4.790	0.949	-0.610	-5.045	**<0.001***	-6.705	-2.875

FVC: Forced vital capacity, FEV1: Forced expiratory volume in the first second,

BDNF: Brain-derived neurotrophic factor * : Statistically significant $P < 0.05$.

Table 5 showed that multivariate linear regression validated the inverse correlation between serum BDNF concentrations and the FEV1/FVC ratio.

Discussion

Respiratory illnesses pose a significant health risk to pesticide workers, with conditions such as lung cancer, asthma, and COPD being more prevalent among those exposed to pesticides, particularly OP compounds (Tarmure et al., 2020).

The present study identified a significant increase in pulmonary manifestations, including coughing, expectoration, wheezing, chest tightness, nasal irritation, and dyspnea among workers exposed to pesticides compared to the unexposed group (Table 1). The results aligned with prior investigations done by Hanssen et al. (2015) who reported prevalence rates of 70.2% for chronic cough and 43.7% for shortness of breath among agricultural laborers in Ethiopia. Additionally, Negatu et al. (2017) documented a higher incidence of pulmonary manifestations, such as chronic wheezing (35.6%) and shortness of breath (44.4%), among exposed farmers in Ethiopia compared to non-exposed individuals.

Similar findings were observed among unexposed farm workers (packing and bundling) compared to those directly involved in pesticide application; Strong et al. (2004) reported a statistically significant increase in pulmonary manifestations, including persistent cough and difficulty breathing, among cutters and welders (odds ratios [OR] of 2.2 (95% CI 1.0 to 5.1) and 1.8 (95% CI 0.9 to 3.8), respectively). They noted that reference personnel involved in packaging and bundling, although unexposed directly, remained potentially exposed to pesticides.

Additionally, Nerilo et al. (2014) from Brazil; reported significantly higher prevalence rates of chest constriction, nasal obstruction, nasal irritation, and cough among agricultural laborers exposed to anticholinesterase insecticides compared to a control group. Similarly, Ohayo-Mitoko et al. (2000) from Kenya; observed a correlation between the use of acetylcholinesterase inhibitors (ACEIs), including malathion, dimethoate, benomyl, metomyia, aldicarb, mancozeb, and propineb, and an elevated incidence of respiratory symptoms such as chest pain, throat irritation, wheezing, and sneezing.

Regarding ventilatory function tests, the current study revealed a statistically significant decline in FEV1%, FEV1/FVC, PEF%, MEF25%, MEF50%, and MEF75% among pesticide-exposed workers compared to unexposed workers. Obstructive patterns were observed in 15.6% of the exposed group but not in any of the unexposed workers, with a statistically significant difference (Table 1). Consistent with these findings, Alif et al. (2017) investigated the correlation between occupational pesticide exposure among middle-aged workers and fixed airflow obstruction. They found a consistent association between all types of pesticide exposure and chronic bronchitis, as well as symptoms indicative of airflow obstruction.

In harmony with the results of the current research, Negatu et al. (2017) from Ethiopia demonstrated a significant decrease in FEV1 among pesticide-exposed workers compared to control groups. Additionally, a study conducted in the Netherlands revealed an exposure-dependent correlation between occupational pesticide exposure and FEV1 reduction (De Jong et al., 2014).

Occupational exposures to OPs have been associated with asthma, asthmatic symptoms, and COPD in numerous epidemiological and clinical investigations (Hernández et al., 2008; Shaffo et al., 2018; Tarmure et al., 2020).

Moreover, FEV1/FVC, a significant indicator of pulmonary function, may decrease in individuals exposed to ChE-inhibiting pesticides, as indicated by a meta-analysis conducted by Ratanachina et al. (2020), pooling results from 56 articles.

The studied exposed group exhibited significantly higher levels of serum BDNF compared to the control group (Table 2). BDNF significantly influences nerve survival, function, and development in both the central and peripheral nervous systems. It has been associated with airway remodeling, a characteristic feature of chronic airway diseases like COPD, and is a crucial mediator of neuronal plasticity in adults (Aravamudan et al., 2012).

On the contrary, a recent investigation by Rodríguez-Carrillo et al. (2022) found a significant correlation between exposure to OP pesticides and reduced levels of serum BDNF.

In the current study, pesticide-exposed workers with obstructive ventilatory dysfunction exhibited significantly higher levels of serum

BDNF (Table 3). Additionally, there was a statistically significant negative association between serum BDNF levels and indicators of obstructive ventilatory function among pesticide-exposed workers (Table 4,5). However, the current findings were consistent with Liu et al. (2023) who observed significantly elevated serum BDNF concentrations in both stable and acute asthma patients compared to individuals without this condition.

Furthermore, BDNF serum levels were reported to be significantly higher in all stages of COPD compared to controls. Stoll et al. (2012) reported specific, stage-dependent relationships between patients' lung function measures and serum BDNF levels.

No correlation was detected between serum BDNF levels and BMI among the studied pesticide workers (Table 4). However, a statistically significant positive correlation was observed between the smoking index, age, and serum BDNF levels among pesticide-exposed workers (Table 4). This finding contradicts the results reported by Sreter et al. (2020), who found no statistically significant correlation between plasma BDNF levels and age, smoking, or asthma patients compared to the control group.

The outcomes of our investigation are consistent with the conclusions drawn in a previous study by Sustar et al. (2019) from India, who found no significant correlation between plasma BDNF levels and BMI. Similarly, Pillai et al. (2012) reported no correlation between plasma BDNF concentration and BMI, but they detected a negative correlation between plasma BDNF levels and age.

Regarding the correlation between smoking and BDNF levels, divergent results have been reported in the scientific literature. Specifically, serum or plasma BDNF concentrations may be lower (Bhang et al., 2010), higher (Jamal et al., 2015), or remain unaltered (Xia et al., 2019) among smokers. It is important to note that research done by Sathish et al. (2013) demonstrated that tobacco smoke increases BDNF and its receptors in airway smooth muscle cells, at least partly as a result of oxidative stress.

Conclusion

There was a significant association between occupational exposure to OP pesticides and the development of airway obstruction. The results of the current study demonstrated a significant increase in BDNF serum levels in pesticide-exposed workers, and workers with obstructive ventilatory dysfunction exhibited significantly higher levels of serum BDNF. Although the exact role of BDNF in the development of airway obstruction in pesticide workers remains unknown, there was a negative association observed in the blood BDNF levels of workers exposed to pesticides and the indicators of obstructive ventilatory function.

Recommendations

The current study represents the initial attempt to examine plasma BDNF as a biomarker for respiratory dysfunction in a national population of workers occupationally exposed to OP pesticides.

Further research is necessary to fully elucidate the mechanisms underlying BDNF's involvement in pesticide-induced airway obstruction and to explore its potential as a therapeutic target for these conditions. Workers in agricultural and related industries should be informed about these risks and take appropriate measures to minimize exposure. Health professionals and policymakers should consider these findings when formulating guidelines and regulations to safeguard the respiratory health of workers exposed to pesticides.

Conflict of Interest

The authors declared no potential conflicts of interest concerning this article's research, authorship, and/or publication.

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