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The Association between Pesticide Exposure and Neurological Signs and Symptoms in Farmers in Magelang District, Central Java, Indonesia

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Abstract

BACKGROUND: Excessive use of pesticides is known to cause neurotoxicity. Chronic effects of pesticide poisoning include neuropathy and tremors.

AIM: This study aimed to determine the association between pesticide exposure and the occurrence of neurological signs and symptoms, especially neuropathy and tremor, in farmers.

METHODS: This was a cross-sectional study. The study location was Seloprojo Village, Ngablak District, Magelang Regency, Central Java Province. Farmers as subjects were recruited to determine neuropathy using Diabetic Neuropathy Symptom (DNS) and Diabetic Neuropathy Examination (DNE) scoring. Tremor events were measured with Tremor Rating Scale (TRS). Cholinesterase levels were examined using venous blood samples to determine the level of pesticide poisoning.

RESULTS: Of the 120 farmers studied, 68.3% experienced pesticide poisoning with cholinesterase levels below normal values. Weakness of the upper limb was found in 10 subjects (8.33%), while weakness of the lower limbs was found in 6 subjects (5%). There were 59.2% farmers who met the neuropathy criteria from the DNS score and those who met the neuropathic criteria from the DNE score were 6.7%. Tremor symptoms were found in 71.7% of the farmers. There was no significant association between cholinesterase levels and DNS score ($p = 0.737$), but there were significantly lower levels of cholinesterase ($p = 0.046$) in the neuropathy group measured with DNE score. There was no significant association between cholinesterase levels and TRS ($p = 0.204$).

CONCLUSION: Cholinesterase levels were significantly associated with neuropathy incidence measured with DNE criteria but statistically not related to tremors in farmers exposed to pesticides.

Introduction

Pesticides had been used widely in agricultural fields to increase crop and food production in Indonesia. Farmers have been using it to control pests and diseases of the crops. In the last three decades, pesticide uses have been increasing extensively [1]. These overuses could lead to many medical problems, including neurological problems [2]. Cholinesterase inhibitors pesticide (i.e., organophosphates and carbamates) are known to reduce the activity of acetylcholinesterase (AChE) [3]. This will result in the increase of acetylcholine concentration in the synapse, which will lead to some nicotinic and muscarinic symptoms and central–peripheral nervous system toxicity [4].

One area known to have significant pesticide poisoning problems is Ngablak, a district in Magelang Regency, Central Java, Indonesia. A previous study showed that 99.8% of farmers in this area had pesticide intoxication ranged from mild to severe [5]. Another study performed in the region showed that 76.47% of farmers classified as having pesticide poisoning by cholinesterase examination. Almost 90% of the farmers used pesticide doses not according to the guidelines. Most of the farmers (75%) did not handle the pesticide correctly [6].

Exposure to pesticide during their application usually causes reversible neurotoxic effects but can also be deadly. The influence of pesticides on the nervous system may be involved in acute toxicity, or it can also contribute to chronic neurodegenerative disorders, especially Parkinson's disease [7], [8], [9]. Some of the chronic effects of pesticide poisoning are weight loss, anorexia, anemia, tremors, headache, dizziness, anxiety, psychological disorders, chest pain, irritability, and cognitive impairment. Organophosphate pesticides that

enter the human body affect nerve function by blocking the enzyme cholinesterase, an essential chemical in delivering impulses along nerve fibers. Thus, one of the effects of pesticide poisoning is the occurrence of disorders of tWhe nervous system, including the central and peripheral nervous system [9]. Pesticides, including organophosphate and organochlorine, have also been shown to be associated with tremor [10].

The objective of this study was to evidence the role of pesticide exposure on the emergence of neurological signs and symptoms, especially neuropathy and tremor, in farmers in Ngablak District, Magelang Regency, Central Java Province.

Methods

Subject selection

This study was an observational analytic study with a cross-sectional design to identify the effect of pesticide exposure, measured through blood cholinesterase levels, on the emergence of neurological signs and symptoms in farmers in Ngablak District, Magelang Regency, Central Java Province, Indonesia. One of the villages in the region, Seloprojo Village, was randomly selected as a study location. The inclusion criteria in this study were: (1) Farmers aged at least 21 years in Seloprojo Village who use pesticides in their agricultural practices and (2) willing to be the subject of research by signing an informed consent after getting an explanation from the research team. Meanwhile, the exclusion criteria in this study were: (1) Having a history of diabetes mellitus, (2) suffering from Parkinson's disease, (3) dementia patients, and (4) chronic alcoholic drinkers.

Measurement of variables

This study used a structured interview questionnaire regarding demographic data, clinical conditions of neuropathy, and risk factors for neuropathy due to exposure to pesticides. Assessment of exposure to pesticides was determined using a questionnaire. A medical examination was done once with the main focus being a neurological examination. The neurological examination consisted of history taking and examination of sensory function, motor strength, physiological reflexes, pathological reflexes, diabetic neuropathy symptom (DNS) score, diabetic neuropathy examination (DNE) score, and tremor rating scale (TRS). Although DNS and DNE were originally developed to detect neuropathy in diabetics, it can also be used to detect neuropathy caused by other reasons. Cholinesterase levels were examined using venous blood samples, which were processed in a private laboratory to determine the level of pesticide poisoning in the research subjects' blood.

Statistical analysis

All data were validated, encoded, recapitulated, and tabulated with means and standard deviation (SD), then entered in the computer using a statistical program. The study received approval from the Health Research Ethics Committee, Faculty of Medicine, Universitas Gadjah Mada.

Results

Subject characteristics

In total, 120 subjects were included in this study with an average age of 48.1 ± 13.6 years. According to gender groups, 93 subjects (77.5%) were male. Most subjects were elementary school graduates (60.8%). Subjects with normal nutritional status (BMI = 18.5–22.5) were 46.7%, overweight (BMI > 22.5) were 46.7%, and only 6.7% had underweight nutritional status (BMI < 18.5). Of all subjects, the average length of work as a farmer was 24.05 ± 15.6 years, with the number of working hours of 6.3 ± 2.3 h/day (Table 1).

Of the 120 farmers studied, 68.3% experienced pesticide poisoning with cholinesterase levels below normal values. Most of the farmers in this study were not in compliance with the use of personal protective equipment (PPE); there were 67 subjects (55.8%) who never used PPE, and only 30 subjects (25%) sometimes used PPE. While according to the duration of using pesticides, there were 82 subjects (68.33%) who used pesticide sprays over 10 years. The majority of farmers (78.3%) spray pesticides routinely with a frequency of 1–2 times/week (Table 1).

Neurological disorders with weakness of the upper limb were found in 10 subjects (8.33%), weakness of the lower limbs was found in 6 subjects (5%). To determine the incidence of neuropathy in subjects, DNS and DNE scoring was used. From the 120 farmers, there were 59.2% who met the neuropathy criteria from the DNS score and those who met the neuropathic criteria from the DNE score were 6.7%. The presence or absence of tremors was measured by the Tremor Rating Scale. Of the 120 farmers, 71.7% had tremor symptoms.

Statistical analysis

Table 2 shows the factors that influence DNS score. It was found that some of the behaviors related to the application spraying of pesticides did

Table 1: Descriptive data of research subjects (n = 120)

Variable	n (%)	Mean (SD)
Age (years)		48.1 (13.6)
Sex		
Male	93 (77.5)	
Female	27 (22.5)	
Level of education		
No school	17 (14.2)	
Graduated from elementary school	73 (60.8)	
Graduated from junior high school	22 (18.3)	
Graduated from senior high school	8 (6.7)	
Length of work as farmers, years		24.05 (15.6)
Number of hours of work, hours/day		6.3 (2.3)
Nutritional status		
Underweight	8 (6.7)	
Normal	56 (46.7)	
Overweight	56 (46.7)	
Compliance using PPE		
Never	67 (55.8)	
Sometimes	30 (25)	
Always	23 (19.2)	
Duration of using pesticides:		
< 1 year	8 (6.6)	
1–5 years	14 (11.7)	
5–10 years	15 (12.5)	
>10 years	82 (68.33)	
Frequency of spraying/week		
≥2 times	6 (5)	
1–2 times	94 (78.3)	
<1 time	20 (16.7)	
Duration of spraying/day		
<5 h	108 (90)	
>5 h	12 (10)	
Upper limb weakness	10 (8.33)	
Lower limb weakness	6 (5)	
Cholinesterase levels		
Normal	38 (31.7)	
Below normal	82 (68.3)	
Upper limb weakness	10 (8.33)	
Lower limb weakness	6 (5)	
DNS examination		
Neuropathy	71 (59.2)	
No neuropathy	49 (40.8)	
DNE examination		
Neuropathy	8 (6.7)	
No neuropathy	112 (93.3)	
Tremor examination		
Tremor	86 (71.7)	
Non-tremor	34 (28.3)	
Blood cholinesterase levels		
Normal	38 (31.7)	
Below normal	82 (68.3)	

DNE: Diabetic neuropathy examination, DNS: Diabetic neuropathy symptom, PPE: Personal protective equipment, SD: standard deviation, n: percentage of participant

not significantly affect DNS results: Including length of working with pesticide (p = 0.924), duration of work (p = 0.065), frequency of spraying (p = 0.804), duration of spraying (p = 0.161), and level of protective use (p = 0.480), There was no significant association between cholinesterase levels and DNS neuropathy (p = 0.737).

Behavior associated with pesticide exposure such as length of working with pesticide, duration of work, frequency of spraying, duration of spraying, and level of protective use was not related to DNE results (p > 0.05) as shown in Table 3. For cholinesterase levels, it was found that there were significant differences between the neuropathy and non-neuropathy groups. The neuropathy group had significantly lower levels of cholinesterase than the non-neuropathy group (7.63 ± 0.805 vs. 8.83 ± 1.82 U/L, p = 0.046).

Tremor rating scale is a measuring tool to determine whether there are tremors or not. From 120 farmers, 71.7% had tremor symptoms. There were no significant differences in tremor incidence in the categories of age and sex (p > 0.05). There were no significant differences in tremor incidence in the categories of age and sex (p > 0.05) (Table 4). Smoking status (p = 0.697) and nutritional status (p = 0.083) also did not have a significant relationship to the incidence of tremors. The use of personal protective equipment (PPE) was not significantly related to the incidence of tremors (p = 0.660). In addition, the level of PPE usage (p = 0.366) and the level of knowledge of pesticides (p = 0.395) did not significantly correlate with the incidence of tremor. The level of cholinesterase was also not significantly associated with tremor incidence (p = 0.204).

Table 2: Factors that affect neuropathy as assessed by DNS score

Variable	DNS results		Ratio (95% CI)	p-value	Average difference (95% CI)
	Neuropathy	Normal			
Mean age, years (SD)	49.08 (14.99)	46.67 (11.3)		0.630	−2.59–7.41
Sex					
Male	51	42	0.740 (0.554–0.989)	0.073	
Female	20	7			
Smoking status:					
Non-smoker	28	13		0.338	
Former smoker	4	3			
Smoker	39	33			
Mean BMI, years (SD)	22.9 (3.57)	22.8 (3.25)		0.979	
Nutritional status					
Underweight	5	3		0.911	
Normal	32	24			
Overweight	34	22			
Level of education					
No school	10	7		0.542	
Graduated from elementary school	40	33			
Graduated from junior high school	15	7			
Graduated from high school	6	2			
Mean length of work as farmers, years (SD)	23.86 (15.27)	24.32 (16.29)		0.924	−6.25–5.34
Mean number of hours of work, hours/day (SD)	6.04 (2.43)	6.77 (2.21)		0.065	−1.59–0.133
Spraying frequency /week					
<1x	12	10			
≥1x	59	39		0.804	
Duration of spraying/day					
<5 h	66	42			
>5 h	5	7		0.161	
Compliance using PPE					
Never	37	30		0.480	
Sometimes	18	12			
Always	16	7			
Mean cholinesterase Levels, U/L (SD)	8.74 (1.89)	8.76 (1.66)		0.737	-0.69 – 0.63
Cholinesterase levels			0.969 (0.701–1.340)	0.847	
Normal	22	16			
Below normal	49	33			

* Significant (p < 0.05); DNS: Diabetic neuropathy symptom; BMI: Basal metabolic index; CI: Confidence interval

Table 3: Factors that affect neuropathy as assessed by DNE score

Variable	DNE results		Ratio (95% CI)	p-value	Average difference (95% CI)
	Neuropathy	Normal			
Mean age, years (SD)	53 (19.3)	47.75 (13.15)		0.577	−10.94–21.44
Sex					
Male	6	87	0.871 (0.186–4.070)	1.000	
Female	2	25			
Smoker status					
Non-smoker	2	39		0.646	
Former Smoker	1	6			
Smoker	5	67			
Mean BMI, years (SD)	22.3 (2.19)	22.9 (3.51)		0.788	−3.03–1.95
Nutritional status					
Underweight	0	8		0.736	
Normal	4	52			
Overweight	4	52			
Level of education					
No school	0	17		0.553	
Graduated from elementary school	6	67			
Graduated from junior high school	1	21			
Graduated from high school	1	7			
Mean length of work as farmers, years (SD)	33 (22.91)	23.4 (14.92)		0.279	
Mean number of hours of work, hours/day (SD)	7.37 (2.66)	6.27 (2.33)		0.203	
Spraying frequency/week					
<1x	7	91		1.00	
≥1x	1	21			
Duration of spraying/day					
<5 h	8	100		0.714	
>5 h	0	12			
Compliance using PPE					
Never	4	67		0.903	
Sometimes	2	28			
Always	2	21			
Mean cholinesterase Levels, U/L (SD)	7.63 (0.805)	8.83 (1.82)		0.046*	−1.92–(−0.48)
Cholinesterase level:			1.10 (1.03 – 1.19)		
Normal	0	38		0.046*	
Below normal	8	74			

*Significant ($p < 0.05$); DNS: Diabetic neuropathy symptom, BMI: Basal metabolic index, CI: Confidence interval, PPE: Personal protective equipment

Table 4: Bivariate analysis of the results from the tremor rating scale

Variable	Tremor rating scale		Ratio (95% CI)	p-value	Average difference (95% CI)
	Tremor	Non-tremor			
Mean age, years (SD)	48.17 (13.58)	47.91 (13.86)		0.896	−5.21–5.74
Sex					
Male	69	24	1.178 (0.862–1.612)	0.254	
Female	17	10			
Smoker status					
Non-smoker	29	12		0.697	
Former smoker	6	1			
Smoker	51	21			
Nutritional status					
Underweight	8	0		0.083	
Normal	42	14			
Overweight	36	20			
Level of education					
No school	14	3		0.300	
Graduated from elementary school	52	21			
Graduated from junior high school	13	9			
Graduated from high school	7	1			
Compliance using PPE					
Never	46	21		0.660	
Sometimes	22	8			
Always	18	5			
Mean cholinesterase Levels, U/L (SD)	8.60 (1.64)	9.13 (2.11)		0.204	−1.25–0.17
Cholinesterase level			0.835 (0.636–1.097)	0.159	
Normal	24	14			
Below normal	62	20			

CI: Confidence interval, PPE: Personal protective equipment

Discussion

The use of pesticides has become commonplace for Indonesian farmers to maintain the quality of crops. However, improper methods of use and a lack of knowledge about pesticides result in excessive exposure of farmers. Of the 120 farmers studied, 68.3% of farmers experienced pesticide poisoning with cholinesterase levels below normal values. This is similar to the Prijanto study [5] performed in the same region showing 71.02% of farmers had been poisoned. Many studies had shown significantly lower cholinesterase levels in pesticide users compared with non-pesticide users [11, 12, 13]. A new study found that the reduction of cholinesterase was not only caused by organophosphate or carbamate [14]. Farmers who used pesticides other than organophosphate or carbamate also had lower cholinesterase levels compared with the unexposed group [15]. The proposed mechanism was organophosphate and organochlorine inhibits pseudocholinesterase in plasma, cholinesterase in red blood cells, and in the synapse, which at certain levels cause poisoning.

In this study, 59.2% of subjects had symptoms of neuropathy identified by DNS. This is higher than

a previous study that showed 37% of farm sprayers complained of sensory symptoms. Other studies from the US and UK showed that intermittent sensory symptoms, mainly in the form of the glove and stocking, were found in 2 to 31% of exposed cases. Signs of neuropathy as assessed by DNE were found in 6.7% of subjects in this study. This is lower compared to a previous study which showed 16% of the subjects had sensory signs. Our study showed that 8% of the farmers have upper extremity weakness and 5% have lower extremity weakness. This is in line with previous studies showing that 0 to 21% of farm sprayers complained of motor weakness [16].

This study showed that blood cholinesterase level, a stable marker of pesticide poisoning, was significantly associated with neuropathy incidence measured with DNE criteria. Cholinesterase inhibitors pesticide (i.e., organophosphates and carbamates) are known to reduce the activity of acetylcholinesterase (AChE) [3]. This will result in the increase of acetylcholine concentration in the synapse which will lead to some nicotinic and muscarinic symptoms and central–peripheral nervous system toxicity [4]. These effects on acetylcholine in synapse could release a high number of glutamate and causing neuronal death because of glutamate excitotoxicity [17]. The mechanism of neuropathy by organophosphate and carbamate usually begins with axonal degeneration followed by secondary demyelination [18]. Organophosphate can also cause delayed neuropathy, which is called Organophosphate-induced Delayed Neuropathy (OPIDN). It is caused by a progressive distal axonopathy of peripheral nerves and spinal cord [19]. The most common cause of OPIDN was acute high-dose intoxication [19]. A chronic low-dose effect on neuropathy has also been proposed.

Pesticide poisoning occurs due to a lack of awareness in the use of PPE and low knowledge concerning the risks of pesticides. One factor that plays a role in causing a decrease in the level of cholinesterase is the length of work as a farmer. In general, the longer working time as a farmer, the greater the level of exposure to pesticides [20]. The duration of exposure to pesticides is also influenced by the frequency of spraying and the use of PPE. If spraying is done with high frequency without being equipped with the use of PPE, then it can affect blood cholinesterase levels in farmers even though the duration of spraying is less than 5 h/day [20]. According to Samosir *et al*., farmers who worked longer than 5 h/day had 2.6 times higher risk to experience balance disorders compared to farmers who worked less than 5 hours per day [21]. Our study did not show an association between duration of exposure, length of spraying per day, and frequency of spraying with the incidence of neuropathy. This will require further study.

Pesticides, including organophosphate and organochlorine, have also been shown to be associated with tremor [10]. However, our study did not show this association. This will also need further study.

Conclusion

This study showed that pesticide poisoning as measured by blood cholinesterase level is associated with neuropathy incidence measured with DNE criteria but statistically not related to tremors in farmers exposed to pesticides.

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