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by Muflihatul Muniroh

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Effect of Chronic Organophosphate Poisoning on Attention Deficit and Memory Impairment

Irene Andriani HALIM[1)], Erni[1)], Ainun Rahmasari GUMAY[2) *)], Saekhol BAKRI[3)], Nani MAHARANI[4)], Muflihatul MUNIROH[2)], Yuriz BAKHTIAR[2)], HARDIAN[2)]

1. *Faculty of Medicine, Diponegoro University, Semarang, Indonesia*
2. *Department of Physiology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia*
3. *Department of Public Health, Faculty of Medicine, Diponegoro University, Semarang, Indonesia*
4. *Department of Pharmacology and Therapeutics, Faculty of Medicine, Diponegoro University, Semarang, Indonesia*

ABSTRACT

Introduction: Organophosphate pesticide poisoning is a common health problem in Indonesia. By inhibiting acetylcholinesterase mechanism, chronic organophosphate poisoning may lead some cognitive consequences included attention deficit and memory impairment. This study investigates the effect of chronic organophosphate exposure in attention deficit and memory impairment. **Method**: A cross-sectional study was conducted in 2 different groups, each consisting of 33 male farmers in Banjarnegara, aged 18-59 years old who are occupationally exposed to organophosphate pesticide for at least 2 years. First group was carried on memory examination using memory impairment screen (MIS) instrument while in second group, attention examination was measured by attention network test (ANT). Vein blood samples analyzed semiquantitatively using Tintometer to know the level of blood acetylcholinesterase (AChE) activity. Data were analyzed using Chi square and Spearman. **Result**: In the first group, 15 (45.5%) samples were found mildly poisioned, while 18 (54.5%) samples were found normal. Among 33 samples, 11 (33.3%) samples have memory impairment. Overall, memory impairment prevalence was higher in sample with mild poisoning, with prevalence ratio of 1,78 (p=0.026). In second group, 54.5% (n=18) farmers were found mildly poisioned while 45.5% (n=15) others had normal AChE activity. Lower AChE activity were significantly correlated with poorer performance in total attention score (r = -0.539; p< 0.00), especially alerting (r= -0.653; p< 0.00) and orienting function (r = -0.632; p< 0.00). **Conclusion.** Chronic organophosphate poisioning seems to have deleterious effects on memory and attention.

Key Words: Organophosphate pesticide, chronic, memory, attention, acetylcholinesterase

Organophosphate pesticide (OP) has toxic property in order to be effective in controlling pest. As its toxic effect, organophosphate has hazardous potential to human and environment.(1) In Indonesia, OP is increasingly used for improving agriculture product quality and quantity.(2) However, this condition is not being followed by proper using of OP.(3) Therefore, Indonesia has high pesticide poisoning rate.

A study had found acute and chronic toxicity in farmers whose exposed by OP. Clinical manifestation of OP pesticide acute poisoning has been well explained and caused by acetylcholinesterase enzyme inbitory. However, study about the correlation of low dose OP chronic expose toward neurobehaviour disruption still inconsistent. Many epidemiological studies said that there is a correlation between OP chronic expose with neurobehaviour disruption.(4–7) As in contrast, other study did not find any correlation between OP chronic expose with neurobehaviour disruption.(8) The aim of this study is to assess the correlation between neurobehaviour disruption, especialy memory impairment and attention deficit in farmers whose exposed by chronic OP pesticide.

MATERIALS AND METHOD

Time and setting of the study

This study was an analytic observational study with cross sectional design. The study was held in Kepakisan village, Banjarnegara in May 2017. Subjects of this study were potato farmers with chronic expose OP pesticide. The test held in the morning in nearby regency office. It was

*Corresponding author: Address: Faculty of Medicine Diponegoro University, Jl. Prof. H. Soedarto, SH Tembalang Semarang,Indonesia. Email: ainungumay@fk.undip.ac.id
Author 1 and 2 has an equal contribution.

choosen for the quiet and comfortable situation of the place so that it will minimize distraction.

Participants

A study was conducted in 2 different groups, each consisting of 33 male farmers in Banjarnegara, who are occupationally exposed to organophosphate pesticide for at least 2 years. An official permission letter had been acquired from nearby village office for cooperation guarantee. Subjects were potato farmers with OP pesticide chronic exposure which had stayed for two years or more in Kepakisan village and had sprayed using OP pesticide within two year or more. Subjects should be male, aged between 18-59 years old, haemoglobin level ≥ 12.5 gr/dl, Body Mass Index (BMI) ≥ 18.5 and at least elementary school graduated or equal. Exclusion criterias was ensured that they had no history or symptoms of any significant disease or conditions including neurologic, kidney and liver; not consuming alcohol habitually; no prescription medication that could inhibit or trigger cholinesterase; and did not agreed to participate in this study.

Tests administered

Subjects that agreed to participate for the research had been explained and asked to sign written informed consent. Furthermore, subjects were asked to fill the questioner about their personal information, job, and medical history. Measuring height and body weight to assess body mass index (BMI). Haemoglobin level evaluation was measured by Haemoglobin Meter. Organophosphate pesticide poisoning rate was assessed by measuring acetylcholinesterase enzyme blood level with Tintometer. Further, subjects were divided into two groups, in group A subject memory was examined using memory impairment screen (MIS), while in group B subject attention level was measured using attention network test (ANT).

RESULT

Table 1. Demographics Status of the Subjects

Characteristics	n (%)		Mean ± SD / median (minimum-maximum)	
	Group A	Group B	Group A	Group B
Age (years)			38.82 ± 8.93 (23-53)	37.73± 10.16 (19 - 57)
Working periode (years)			15 (3-30)	11 (3 - 37)
BMI			23.3 (18-33.6)	24.05 ± 3.26 (18.5 – 32.9)
Hb			14.6 (13.4-17.1)	14.71 ± 0.84 (13.4 – 17.1)
Education				
Junior high school	18 (54.5%)	22 (66.7%)		
Senior high school	13 (39.4%)	10 (30.3%)		
Bachelor	2 (6.1%)	1 (3%)		
Self Protection				
Fully equipped	28 (84.85%)	30 (90.91%)		
Not fully equipped	5 (15.15%)	3 (9.09%)		

Group A

There were 33 subjects in this study which suited the inclusion and exclusion criterias. Potato farmers age mean was 38.82 ± 8.93 with the youngest age was 23 years old and the oldest 53 years old. No subjects had body mass index and haemoglobin level less than normal. Beside that, farmers work time median was 15 years with the least time was 3 years and 30 years the longest. From 33 subjects, there were only 5 subjects used personal general precaution properly.

Group B

In group B, there were also 33 subjects which suited inclusion and exclusion criterias. Subject age mean was 37.73 ± 10.16 with the youngest age

was 19 years old and the oldest was 57 years old. No subjects had body mass index and haemoglobin level less than normal. While, work time variable which had abnormal distribution resulted in median value between 11 years with the least work time 3 years and the longest was 37 years. From 33 subjects, there were only 3 subjects used personal general precaution.

Table 2. Acetylcholinesterase enzyme level examination

Acetylcholinesterase activity	n (%)	
	Group A	Group B
Normal	18 (54.5%)	14 (57.6%)
Low poisoning rate	15 (45.5%)	19 (42.4%)

Group A

Poisoning rate characteristic was assessed with acetylcholinesterase enzyme blood level activity. Normal cut off for acetylcholisnterase enzyme blood level was ≥ 75%, low poisoning 75%-50%, moderate poisoning 50-25%, and severe 25%-0%. There were 15 subjects had low poisoning rate, while other 18 subjects was normal.

Group B

From 33 subjects, 57.6% or 19 people had low poisoning rate, while other 42.4% or 14 people were normal.

Memory and attention examination

Group A

Memory function characteristic measured by memory impairment screen (MIS) score with the scoring was >7.5 (memory impairment) and <7.5 (no memory impairment).(10) There were found 11 subjects had memory impairment (33.3%) and 22 subjects (66.7%) had no memory impairment.

Group B

Attention level characteristic data had abnormal distribution with alerting function median value was 33 which the lowest was -36 and the highest was 141, orienting function median value was 40 which the lowest was -15 and the highest was 138, while median value of executive control was 143 with 48 as the lowest and 442 as the highest. Total attention level median value was 195 with minimal score 27 and maximal score 721.

Correlation between acetylcholinesterase with memory function and attention level

From 15 subjects that had low poisoning rate, 8 subjects encountered memory impairment, while 18 sample were clear from poisoning, only 3 subjects had memory impairment. Hypothesis test used in this study was *Chi- Squared* test, with p value 0.026. There was a significant correlation between acetylcholinesterase enzyme activity category with memory function which the prevalence ratio was 1.78.

Table 3. The attention examination using Attention Network Test (ANT)

Characteristic	Median (minimum-maximum)
Alerting	33 (-36 – 141)
Orienting	40 (-15 – 138)
Executive control	143 (48 – 442)
Total attention	195 (27 – 721)

Table 4. Correlation between acetylcholinesterase with memory function

Acetychilinesterase activity	**Memory catagory**		**p***
	No memory impairment	**Memory impairment**	
Normal	15	3	0.026
Low poisoning rate	7	8	

*RP: 3.18

Table 5. Correlation between acetylcholinesterase with attention level

	Acetylcholinesterase activity	
	Correlation coefficient	P value
Alerting	-0.65	< 0.01
Orienting	-0.56	< 0.01
Executive	-0.20	0.27
Total Attention	-0.47	0.01

There was a negative correlation between acetylcholinesterase blood activity and total attention level, alerting function and also orienting function whi the corelation rate consecutively was -0.47 (p = 0.01), -0.65 (p < 0.01) and -0.56 (p= < 0.01). Thus, acetylcholinesterase blood activity had moderate negative correlation rate toward total attention level and orienting function, also high negative correlation rate toward alerting function. Beside that, statistically *executive control* function showed unsignificant low negative correlation rate (r = -0.20; p = 0.27).

DISCUSSION

Blood acetylcholinesterase activity was one of the organophosphate toxication markers which was easy to be measured. The low activity of blood acetylcholinesterase indicated a magnitude of organophosphate effect in inhibiting acetylcholinesterase enzyme.

The result showed that there was a correlation between chronic exposure of organophosphate pesticide to memory and attention function. Based on statistic test, farmers in group A who suffered from low poisoning rate of organophosphate pesticide had 3,38 times chance more often to have memory impairment. It assessed memory function of subject especially recall ability. While in the group 2, the result showed significant negative correlation between acetylcholinesterase and attention especially in alerting and orienting function after tested using Spearman test. This study was in accordance with some previous studies which state that chronic exposure of organophosphate pesticide would cause memory and attention impairment. (4–7)

Malekirad et al in 2013 found decreasing memory, attention, spatial function, psychomotor speed together with inceasing incidence of anxiety, depression and insomnia in chronic-organophosphate-exposured farmers compared to the control. Those neuropsychiatric symptoms called by *Chronic organophosphate-induced neuropsychiatric disorder* (COPIND) as a result of low dose chronic organophosphate exposure without being started with cholinergic syndrome.(10)

The primary mechanism of organophosphate toxicity was the inhibition of acetylcholinesterase enzyme. Aboudonia stated a hypothesis about organophosphorus ester-induced chronic neurotoxicity (OPICN) which caused necrosis and apoptosis of the brain cells through the accumulation of acetylcholin in the central nervous system. The oversimulated acetylcholin receptor (mACh would produced excitotoxin which activate NMDA (N-methyl-D-aspartate) subtype of glutamate receptors. It lead to a massive influx of calsium ions to the postsynaptic cell and disturb its homeostasis. Then free radical was produced and the intracelular component was degraded, resulting neuronal degradation.(11) This early lesion then would produce secondary lesion through inflammation and oxidative stress cascade which induced apotosis of the other neuron and escalate the damage.(10) Organophosphate toxicity also having direct effect on increasing oxidant and decreasing antioxidant, leading to neuronal death and gene expression alteration.(12)

Nevertheless, chronic poisoning mechanism was not limited only in that inhibition process, some studies had proven that there were other mechanisms took in charge. As in result, memory and attention function impairment mechanism caused by chronic exposure of organophosphate pesticide was not only limited by acetylcholinesterase enzyme inhibition.(13)

Blood Brain Barier Impairment(14)

In healthy nervous system, blood brain barrier consist of endothelial cells forming a tight junction to detain big molecules. Brain traumatic injury, hipoxia, and other chemical substances, such as organophosphate pesticide would increase this permeability of blood brain barrier.

Cytotoxicity(10,14,15)

Low dose of OP chronic exposure would cause gradually cell death from the effect of free radical formation or *reactive oxygen species* (ROS). Organophosphate pesticide induced mithocondria damage as of morphology disruption and decrease in mithocondria cell amount. This would cause adenosine triphosphate (ATP) depletion and ROS formation enhancement leading to oxidative stress. ROS induced a fatal ATP mithocondria depletion, activated proteolytic enzyme, and DNA fragmentation, at the end leading to cell apoptosis.

Axonal Transport Impairment(15)

Organophosphate pesticide might disrupt fundamental neuron process, axonal transporting. Axonal transporting was responsible in lipid mobilization, mithocondria, synaptic vesicle, mRNA, enzyme, protein receptor, *growth factor,* and some macromolecules transporting from neuronal cell body to cytoplasm troughout axon and otherwise. Axonal transport disruption process was identified in some neurologic diseases such as, *amyotropic lateral sclerosis, Alzheimer's disease, Huntington's disease, and Pick's disease.*

Neuroinflamation(14)

Organophosphate pesticide would provoke gliosis process. Gliosis is an inflammation respond from the brain as a result of neuron damage. Those inflammation respond usually exhibit a hipertrophy and proliferation of glial cell, especially astrocyte and microglia. This microglia activation accompanied by proinflammatory cytokine enhancement.

Yet this result also found an insignificant correlation between blood acetylcholinesterase and executive control. Executive control consist of planning and decision making, assosiated with dopamin activating process in cyngulus anterior cortex, basal ganglia and lateral prefrontal cortex.(16)(17) Those result was different with an experimental study in rats exposed by organophosphate, which the result showed there was a decline in dopamin level inside basal ganglia.(18)

Many factors that could affect this study result were diet, smoking and technical factor, as executive control measurement test had the highest difficulty level task, wherefore it was possible to have understanding biased among the subjects. Beside that, subjects heterogenity in terms of computer operating skill caused wide data variation in which the subject who able to operate computer fluently had shorter measurement time, as in contrast, subject who unable to operate computer had longer measurement time result.

A spesific study that assessed organophosphate effect to each components of attention function still had not been found so that the underlying mechanism was still unclear. The hypothesis still attributed to inhibitory of acetylcholinesterase inhibition and other mechanisms as described before.

Limitation

The limitation in this research was the design of the study, considered to be frail showing correlation between the variables. Cross sectional design was choosen as for the time and distance impediment. Inability to monitor any potential factor that might affect the result optimally, such as computer operating skill, wherefore attention level data had wide variations. Another inadequency was the instrument used in assessing acetylcholinesterase was tintometer and attention measurement instrument had long duration and repetitively.

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