Neurocognitive impairment, Mental health status clinical and biochemical toxicity biomarkers in farmers exposed to organophosphate pesticides

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Abstrat

The aim of this study was to study toxicity of organophosphate (OP) pesticides in exposed farmers in terms of neurocognitive impairment, Mental health status, clinical symptom, diabetes and hematological factor. A comparative cross-sectional analysis was done in 174 farmers who have been exposed OPs in comparison to a control group containing 174 healthy subjects with the same age and sex and education level. The levels of Fasting blood glucose, Blood urea nitrogen(BUN), cholesterol, triglycerides, **Creatinine**, High-density lipoprotein (HDL), Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) and alkaline phosphates (ALKp) were measured in the blood of subjects. The mean level of Fasting blood glucose, BUN, cholesterol and ALT was significantly raised in workers while **Creatinine**, triglycerides and Alkalin phosphatase significantly decreased as compared with controls. The mean levels of AST and Fbs2 in the workers and controls were not statistically different. The neurocognitive impairment and psychological disorders were significantly raised in workers..Clinical examination was done in order to record any abnormal sign or symptoms. Farmers showed clinical symptoms such as eczema, saliva secretion, fatigue, headache, sweating, abdominal pian, ,nausea , disfoghani, distahtani, protahtani, azolate shekami, hand tingling, foot tingling, epiphoria, edrar, myosis, dyispnea, bradycardia, nasal flowing. The present findings indicate that inhibition of AChE can be incidence of neuropsychological disorders and pre diabetes. Use of supplementary antioxidants would be useful in the treatment of farmers.

Keywords: Organophosphate, Neurocognitive impairment, Mental health status, Diabetes

Introduction

The latest estimate by a WHO task group indicates that there may be 1 million serious unintentional poisonings each year and in addition 2 million people hospitalized for suicide attempts with pesticides. This necessarily reflects only a fraction of the real problem. On the basis of a survey of self-reported minor poisoning carried out in the Asian region, it is estimated that there could be as many as 25 million agricultural workers in the developing world suffering an episode of poisoning each year(Jeyaratnam, 1990). Anticholinesterase compounds, organophosphates (OPs) and carbamates (CMs) are commonly used for a variety of purposes in agriculture and in human and veterinary medicine. They exert their toxicity in mammalian system primarily by virtue of acetylcholinesterase (AChE) inhibition at the synapses and neuromuscular junctions, leading into the signs of hypercholinergic preponderance.

However, the mechanism(s) involved in brain/muscle damage appear to be linked with alteration in antioxidant and the scavenging system leading to free radical-mediated injury(Milatovic et al .,2006). In both type 1 and type 2 diabetes, diabetic complications in target organs arise from chronic elevations of glucose. The pathogenic effect of high glucose, possibly in concert with fatty acids, is mediated to a significant extent via increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and subsequent oxidative stress (Evans et al., 2003). Careless use of pesticides like organophosphate (OP) insecticides may causes diverse health complications by upsetting the nervous, endocrine, reproductive, and immune systems (Soltaninejad and Abdollahi, 2009). World Health Organization (WHO) approximation is that around one million severe unintentional and two million intentional poisoning with insecticides come about worldwide, and of these almost 220,000 die (WHO, 1997). The pathogenesis of type 2 diabetes is complex, with two distinct mechanisms: insulin resistance (decrease of insulin action on peripheral tissues) and insulin deficiency (impaired insulin secretion by pancreatic beta-cells). These abnormalities are due to genetic and environmental factors (Pinget and Boullu-Sanchis, 2002;Rezg et al., 2010). The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030(Wild et al., 2004). Many studies provides support that POP exposure might contribute to type 2 diabetes mellitus (Abdollahi et al 2004; Turyk et al.,2009;Ukropec et al 2010; Rignell-Hydbom et al 2009; Ruckmani et al 2011; Codru et al 2007; Teimouri et al.,2006;Slotkin, 2011;Hectors et al., 2011).On the other hands, the overall evidence of neurologic and neurobehavioral effects of long-term OP exposure was small. Some study reported that many environmental neurotoxicants that have been shown to produce developmental neurotoxicity include polychlorinated biphenyls (PCBs), dioxins, pesticides, ionizing radiation, environmental tobacco smoke, and maternal use of alcohol, tobacco, marijuana and cocaine. Exposure to environmental agents with neurotoxic effects can result in a spectrum of adverse outcomes from severe mental retardation and disability to more subtle changes in function depending on the timing and dose of the chemical agent (Mendola et al 2002). All of which support the existence of a positive link between exposure to OP and neurotoxicity (Karami-Mohajeri and Abdollahi,2011;Rohlman et al., 2011;Jamal et al., 2002; Salvi et al., 2003; Eskenazi et al., 2007; Marks et al., 2010; Lotti and Moretto ,2005; Ranjbar et al., 2010). Typically, OPs have been defined as inhibitors of acetyl cholinesterase (AChE) but they can also act through non-cholinergic pathways (Teimouri et al. 2006). For instance, the enzyme acylpeptide hydrolase was shown more sensitive than AChE to some OPs, such as dichlorvos, which is the parent compound for metrifonate, a therapeutic agent used in the treatment of cognitive impairment (CI) together with AD. However, the direct action of acylpeptide hydrolase in cognitive processes and the physiological and molecular effect of OP have not been determined yet (Pancetti et al., 2007). Also, OPs can inhibit the enzyme neuropathy target esterase (NTE) that results in lower-limb paralysis and distal injury in long nerve axons (Gupta 2009). Totally, OPs cause four important neurotoxic effects in humans: the cholinergic syndrome, the intermediate syndrome, delayed polyneuropathy, and chronic neuropsychiatric disorder (Jokanović and Kosanović, 2010). OPs in chronic toxicity produce free radicals and disturb body oxidant/antioxidant status that results in cell wall damage and cell nuclear toxicity (Ranjbar et al., 2002;Bayrami et al.,2012).The health effects of acute exposure to pesticides are characterized very well but the long-term health effects among exposing people after a chronic low-level exposure is under question. The present study was planned to scrutinize the neurocognitive impairment, Mental health status, clinical symptom, diabetes and hematological factor in farmers exposed to OP pesticides.

Study population

A relative cross-sectional study with a total number of 374(252 male,122 female) subjects was accomplished. All subjects gave informed consent before the beginning of the study and the approval of the study protocol by the Institute Review Committee. The first cohort included 187 horticulture farmers, with age range of 16-80, who worked as farmers around a village named Hafte in the South-West of Shiraz, Iran. Control subjects were selected from the same village consisting of 187 workers who were not engaged in any agricultural work and had no history of job-related exposure to OP pesticides. Information on working history, socioeconomic status (salary, education), and lifestyle information (smoking, alcohol consumption, drug uses, consumption of vitamin or antioxidant supplements, and dietary habits) were achieved by a questionnaires completed in a conversation between the subject and an expert examiner. Neurocognitive impairment was measured by Subjective Neurocognition Inventory (SNI) and Mental health status evaluated by General Health Questionnaire (GHQ-28) (Moritz et al., 2004; Goldbeg and Williams, 1988). All subjects were submitted to comprehensive clinical examination to identify any signs or symptoms of long-lasting illnesses such as arterial hypertension, heart failure, cancer, thyroid disturbance, asthma, diabetes, and anemia. Those with chronic disease, alcohol consumption, antioxidant consumption, and/or under drug usage, or contact to poisonous materials, radiation therapy, or substance abuse were left out from the study. Blood samples were collected from counted in subjects throughout the course of a spraying season between 7 and 8 AM before arriving the place of work on Saturday as the beginning of the weekly work. The levels of Fasting blood glucose,Urea, cholesterol, triglycerides, cratinin, High-density lipoprotein (HDL), Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) and alkaline phosphates (ALKp) were measured.

Subjective Neurocognition Inventory (SNI)

The self-report questionnaire consists of 76 items with a focus on everyday memory and attention problems. Part of the questionnaire is the “Fragebogen Erlebter Defizite der Aufmerksamkeit” (FEDA, Questionnaire for the measurement of self-experienced deficits of attention), a questionnaire that taps attentional difficulties (Zimmermann et al., 1991). This scale was complemented by new items constructed by Moritz et al. Items had to be endorsed on a five-point likert scale (very frequently-never). The following domains were tested: selective attention (10 items), divided attention (4 items), long-term memory (7 items), prospective memory (7 items) and psychomotor retardation (9 items). One item tapped the forgetting of names (for a more through description (Moritz et al. , 2004).

General Health Questionnaire (GHQ-28)
The Iranian version of the General Health Questionnaire (GHQ28) was used to identify high risk subjects for mental disorder, as well as the following four symptoms: "somatic symptoms", "anxiety and insomnia", "social dysfunction", and "severe depression"(Goldbeg and Williams 1988).

Statistical analysis

All data were analyzed with Stats Direct 2-7-8.Two-sample t test and data. Multivariate analyze variance were used for statistical comparisons after plotting and testing for equal variances. Pearson correlation coefficient was used to study the association between variables. All data are presented as mean+SD. p Values lower than 0.05 were considered statistically significant.

Results

Table 1 shows the average levels of subjects ages, years of employment, smoking habits (years and N/day), and sex. There was no statistically significant difference between two groups in terms of age and years of employment but smoking habits significantly different in workers and controls.

Table 3 shows that somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression in workers and controls. The rate of anxiety and insomnia, and severe depression in workers were significantly increased as compared with controls.

Table 3 shows that Psychomotor Speed (PS), Selective Attention (SA), Divided Attention (DA), Verbal Memory (VM), Nonverbal Memory (NVM), Prospective Memory (PM), Spatial Functioning (SF) and Initiative/Energy (I/E) were significantly decreased in workers as compared with controls.

Table 4 shows the average levels of Fasting plasma glucose, Blood urea nitrogen(BUN), cholesterol, triglycerides, **Creatinine**, High-density lipoprotein (HDL), Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) and alkaline phosphates (ALKp). The mean level of Fasting blood glucose, Urea, cholesterol and ALT was significantly raised in workers while **Creatinine**, triglycerides and Alkalin phosphatase significantly decreased as compared with controls. The mean levels of AST and Fbs2 in the workers and controls were not statistically different.
There were a positive correlation among number of working year on one side and eczema (r^2= 0.26, p <0.0001), saliva secretion (r^2= 0.268, p <0.0001),fatigue (r^2= 0.296, p <0.0001),headache(r^2= 0.31, p <0.0001),sweating (r^2= 0.149, p <0.005),abdominal pian (r^2= 0.162, p <0.002),nausea(r^2= 0.229, p <0.0001),disfoghani(r^2= 0.21, p <0.0001), distahtani(r^2= 0.193, p <0.0001),protahtani(r^2= 0.158, p <0.003), breath muscle weakness (r^2= 0.115, p <0.030),hand tingling (r^2= 0.297, p <0.0001),foot tingling (r^2= 0.298, p <0.0001), epiphoria (r^2= 0.279, p <0.0001),edrar(r^2= 0.136, p <0.01),miosis (r^2= 0.107, p <0.044),dyispnea (r^2= 0.239, p <0.0001),bradycardia (r^2= 0.17, p <0.001),nasal flowing (r^2= 0.218, p <0.0001on the other side.

Table 1. Summary of demographic data in workers and control subjects

Subjects	Farmers (n= 174)	Controls (n= 174)	p Value
Age (years)	37.94±12. 41	37.05±11.78	0.48
Sex	126(Male) 61(Female)	126 (Male) 61(Female)	-
Work history (year)	9.78±7. 72	-	
Smoking (years)	0.39 ±2.45	1.36±5.3	0.026
Smoking (N/day)	0.62±3.75	1.07±4.1	0.27

Data represent mean ± SD.

Table 2. The status of somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression in workers and controls

Group	somatic symptoms	anxiety and insomnia	social dysfunction	severe depression	GHQT
Farmer	7.97±4.23	8.07±4.29	6.7±3.28	7.08±4.95	29.92±12.63
Control	7.30±3.22	6.47±2.51	7.68±2.35	4.73±2.36	25.91±6.45
df	1	1	1	1	1
F	611.061	633.42	971.41	343.76	1146.78
pValue	0.28	0.007	0.13	0.0001	0.016

Table 3. The status of Neurocognitive impairment in controls and workers

Group	PS	SA	DA	VM	NVM	PN	SF	IE	Total
Farmer	23.68±6.31	29.47±7.77	14.2955±4.89	26.55±7.34	14.44±4.87	23.49±5.75	14.16±5.68	35.90±9.78	247.57±47.25
Control	31.15±3.16	43.34±5.49	17.98±3.20	34.58±4.26	17.70±2.78	30.84±3.6	18.24±4.84	47.11±6.73	332.40±32.15
df	1	1	1	1	1	1	1	1	1
F	98.60	187.29	34.92	78.95	29.79	102.98	26.32	78.59	

									193.93
pValue	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

PS: psychomotor speed; SA: selective attention; DA: divided attention; VM: verbal memory; NVM: nonverbal memory; PM: prospective memory; SF: spatial functioning; and I/E: initiative/energy

Data represent mean ± SD.

Table 4. Hematological parameters in controls and workers

Group	Fasting plasma glucose (mg/dL)	**BUN**(mg/dL)	**Creatinine**(mg/dL)	Cholesterol (mg/dL)	Triglycerides (mg/dL)	HDL (mg/dL)	AST (IU/L)	ALT (IU/L)	ALKp(IU/L)	Oral glucose tolerance test(mg/dL)
Control	76.95± 27.66	28.38± 9.50	.86±.13	160.27 ±32.47	136.78 ±92.82	47.03± 10.90	30.82± 10.16	20.02± 8.26	114.23± 43.388	**86.29±** 24.97
Farmer	84.89± 13.59	30.64± 10.3	.82±.183	174.50 ±43.72	123.59 ±53.43	44.85± 7.47	24.26± 10.2	20.19± 13.32	93.14±2 7.78	**86.27±** 14.48
pValue	0.001	0.027	0.0001	0.015	0.0001	0.0001	0.49	0.001	0.015	**0.99**

Discussion

The results of this study show that Neurocognitive impairment and psychological distress and the level of Fbs, Urea, cholesterol and ALT were significantly higher in the farmers as compared with controls, while the cratinin, triglycerides and Alkalin phosphatase level in workers were lower than controls. As the first thought, it can be said that exposure to OP pesticides in the farmers has resulted in the production of free radicals and oxidative stress. The positive correlation between working history and clinical symptoms confirms existence of pollution and also absorption of this pesticide into body. In interview with farmers, it was found that they did not use proper protection tolls like mask, gloves, long boots, head cover, face cover, and they did not take shower in a regular manner. The only safety tools that they used were a kind of cloth masks.

A study showed a significant positive correlation between working history and clinical symptoms in organs like respiratory, ocular, gastrointestinal, and skin in pesticide sprayers (Singh et al., 2006). The present study workers also complained some of pesticide poisoning symptoms.

In the present study, there were a raised significant in neurocognitive impairment and psychological distress in farmers. In support, there are some study reporting increasing association between low levels of pesticide exposure and deficits in neurobehavioral performance(Rothlein et al.,2006). Another study reported that Exposure to low levels of pesticides over many years of agricultural work is associated with neurological impairment as measured by the Selective Attention, Symbol-Digit, Reaction Time tests. Experience handling pesticides was also associated with deficits in neurobehavioral performance (Rohlman et al., 2007). Another work provides powerful evidence in favor of a causal relationship between OP exposure and significant neuropsychiatric disorder including mood destabilization and CI (Davies et al., 1999). Actually, most of studies reported previously indicate incidence of neuropsychological disorders in occupationally OP-exposed workers (Rosenstock et al., 1991; Fiedler et al., 1997).It seems that large toxic doses of organophosphorus compounds cause acute necrotic neuronal cell death in the brain, whereas sublethal or subclinical doses produce apoptotic neuronal cell death and involve oxidative stress and on the other hands OPs can inhibit the enzyme neuropathy target esterase and acylpeptide hydrolase and these are causes for neurocognitive disorders.

The present findings about increased of Fasting blood glucose is in agreement with the previous studies on workers who were chronically exposed to OP pesticides (Rezg et al., 2007). In rodents it has been demonstrated that small doses of bisphenol-A have profound effects on glucose metabolism. Therefore, this altered blood glucose homeostasis may enhance the development of type 2 diabetes(Alonso-Magdalena et al.,2010).Another study reported that Several POPs at low doses similar to current exposure levels may increase diabetes risk, possibly through endocrine disruption (Lee et al., 2010).Other study reported that Simultaneous exposure to various POPs in the general population may contribute to development of obesity, dyslipidemia, and insulin resistance, common precursors of type 2 diabetes and cardiovascular diseases. Although obesity is a primary cause of these metabolic abnormalities, POPs exposure may contribute to excess adiposity and other features of dysmetabolism (Lee et al., 2011). Moreover sub chronic malathion exposure causes progressive hyperglycemia which can be a risk factor for diabetes(Ruckmani et al., 2011).Also Increasing serum concentrations of individual POPs considerably increased prevalence of prediabetes and diabetes in a dose-dependent manner. Interaction of industrial and agricultural pollutants in increasing prevalence of prediabetes or diabetes is likely(Ukropec et al., 2010).Taken together, these findings provide other evidence that OPS has the propensity to impair glucose homeostasis, also may induce diabetes associated with stimulation of hepatic gluconeogenesis and glycogenolysis in favor of glucose release into the blood.

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