IMMUNOTOXICITY OF SOME PESTICIDES IN EGYPTIAN DIABETIC CHILDREN

BY

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ABSTRACT

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder that could be triggered by environmental pollutants in genetically susceptible individuals. The present study aimed to assess the immune response of different lymphocyte subpopulations in a group of diabetic children in relation to pesticides with highest Odds ratios (lindane and malathion). One hundred and ten Egyptian children; their ages ranged from 1.2 to 10 years were studied. The control group comprised 35 healthy children, while the study group included 75 children (diagnosed as T1DM within the first month). Seven whole peripheral blood sample was collected from each child and was divided as follows: 5 ml blood was taken for toxicological analysis of pesticides residues using Gas Chromatography equipped with Ni^{63} Electron Capture Detector. The remaining 2 ml blood sample was collected in EDTA tubes and used immediately for testing immunological markers by using flowcytometry. The results revealed significant correlation as regards the expression of CD4 %, HLADR % and CD4/CD8 ratio in relation to lindane. While malathion (an organophosphate compound), shows a significant correlation with CD4 %, CD20 %, CD16 % and HLDAR % lymphocyte subsets in the diabetic group compared to healthy subjects. It is concluded that pesticides might play a role concerning the increased incidence of T1DM in children.

Keywords: *Pesticides, Childhood Diabetes, Immunotoxicity.*

INTRODUCTION

Immunotoxicity is an important area for human risk assessment. This helps to identify environmental toxicants that can potentially impact the immune system of exposed individuals and allows studying the association between immune modulation and diseases (Taylor and Pauels, 2006; Abadin et al., 2007).

Current evidence suggests that the immune system is a target for the toxic effects induced by several types of pesticides leading to various immune disorders such as immunodeficiency, tumorigenesis, allergies, and autoimmunity (Wang et al.,

2007; Ward et al., 2009; Fukuyama et al., 2010).

Type 1 diabetes mellitus (T1DM) is one of the commonest chronic health problems in children. A steady increased incidence of this autoimmune disease has been reported. This could be explained by environmental factors that possibly trigger or accelerate the autoimmune process in genetically predisposed subjects (Harrison et al., 2008; Van Belle et al., 2011).

The immune response plays a critical role in the development of T1DM. It is assumed that studying the effects of toxicants such as pesticides on the children's developing immune system is of utmost importance (Holsapple et al., 2004; Duramad et al., 2007).

Lymphocyte subsets counts serve as a general test of the immune status. Moreover, determination of the expression of lymphocyte clusters of differentiation such as CD3, CD4, CD8 and CD16 positive cells is worthy as it could assess the balance between lymphocyte subpopulations and highlight any modulation helping to identify the types of memory T helper (Th1 or Th2) cells generated due to a specific antigen exposure (Colosio et al., 2005; Molinier et al., 2011).

Few studies were conducted to assess immune disorders associated with different diseases using flowcytometry (Duramad et al., 2007; Harrison et al. 2008). Therefore, accurate enumeration and functional assessment of auto reactive CD8+ T cells with effective discrimination between patients with T1DM and non-diabetic subjects may be useful for tracking the autoimmune process and trying to stop its progression (Cernea and Herold, 2010; Todd, 2010).

As far as we aware, this is the first study aiming to assess the immune response regarding different lymphocyte subpopulations in relation to pesticides in a group of T1DM children.

MATERIAL AND METHODS

(1) Patients :

This study was conducted on 110 children who were presented with their mothers to Mansoura University Children Hospital, Endocrinology and Diabetes Unit. The study began at September 2008 and ended by April 2010 when the targeted cases were collected. They were divided into two groups:

A. Study group: 75 children aged more than one year and ≤ 10 years who were newly diagnosed as type 1 diabetes (within the first month) and fulfilled the inclusion criteria.

B. Control group: 35 healthy children who came with their mothers and their

diseased siblings to the Pediatric clinic in Mansoura University Children Hospital.

C. Exclusion criteria:

1. Children with family history of diabetes, allergy, atopy, asthma or any associated autoimmune disease.

2. Any child with associated disease, birth defect, physical or mental retardation, or congenital anomalies e.g. cardiovascular or musculoskeletal.

3. Any other medical condition associated with T1DM.

(2)Sampling:

- Approval from the Ethical Committee of Mansoura University-Faculty of Medicine was taken for carrying on the research besides an informed consent from mothers of the studied children to participate in the research.

- Seven ml whole blood sample was collected from each child. It was divided as follows: 5 ml blood was precipitated for 30 min. and centrifuged at 3600 round per minute (rpm) for 15 min. Then, all serum samples were stored at -70^{o}C until toxicological analysis of pesticides residues was done. The other 2ml was used to perform blood and immunological investigations.

(3)Measurement of pesticides levels:

- **Extraction and instrumentation:**

Extraction of pesticides residues from different collected samples was done according to the method of Liu and Pleil (2002). The extracted samples were analyzed by Hewlett Packard Gas Chromatography (GC) Model 5890 equipped with Ni^{63} Electron Capture Detector (ECD), and fitted with HP- 101capillary column.

(4)Blood and immunological analysis:

Two ml blood was collected in EDTA tubes as an anticoagulant and immediately transported to the clinical pathology Laboratory, Flowcytometry Immunophenotyping Unit, Faculty of Medicine, Mansoura University for doing complete blood picture, assessment of Leishman-stained peripheral blood smears and for surface antigens staining.

Flowcytometric analysis:

Measurement of lymphocyte phenotypic subsets was done by indirect immunofluorescence using monoclonal anti-human antibodies. For surface antigens staining, blood samples were lysed using lysine solution, washed with phosphate buffered saline (PBS) once or twice until complete RBCs lysis and then resuspended in appropriate amount of PBS. The cells were stained with different fluorescently labeled monoclonal antibodies (mAb) according to manufacturer instructions (Dakocytomation, Denmark

and Beckman Coulter, France).

Different mAb against the following surface antigens were used : CD3 (total-T cells), CD4 (helper/inducer), CD8 (suppressor/cytotoxic), CD20 (B-cells), CD16 (Natural Killer cells) and HLADR (activated T-cells). The immunophenotyping was performed on EPICS-XL four color flowcytometry (Coulter, Miami, Fl). The cells were analyzed with the most appropriate lymphocyte gate using the combination of forward and side scatters. An antigen was considered positive when the expression is at least 20% of the gated cells. Negative isotopic controls were used to determine the non-specific binding. Total white cell counts and lymphocyte counts were determined on whole blood using a Coulter Cell Counter.

Statistical analysis:

The statistical analysis of data was done by using excel program for figures and SPSS (SPSS, Inc, Chicago, IL) program statistical package for social science version 16. Quantitative data were presented as mean ± standard deviation (SD) and frequency for normally distributed groups. Whereas quantitative data for groups with abnormal distribution were presented as mean, median; minimum; maximum and frequency. The analysis of data was done to test statistical significant difference between groups. For quantitative data, student t-test was used to compare between two groups. Chi square test (χ^2) was used for qualitative data. P is significant if ≤ 0.05. Odds ratios and corresponding 95% confidence interval (CI) were calculated to estimate the magnitude of association between independent variables.

RESULTS

The concentrations of pesticides residues in the studied groups and their odds ratios (OR) are illustrated in table (1).

The investigated immunological markers in the studied groups are demonstrated as mean ± SD in table (2). A highly significant difference between the control group and diabetic children is found regarding the following: WBCs, lymphocytes%, absolute lymphocytic count (ALC), expression of (CD3%, CD4%, CD8%, CD16% HLADR%) and CD4/8 ratio. On the other hand, no significant difference is seen concerning CD20 % expression.

The correlation between those pesticides residues and both white blood cell count and different lymphocyte markers in the diabetic and control groups of children is demonstrated in table (3). As regards organocholrine compounds, a significant association is found concerning the expression of CD4%, HLADR% and CD4/CD8 ratio in relation to lindane.

While malathion (an organophosphate compound), shows a significant correlation as regards CD4 %, CD20 %, CD16 % and HLADR % expression.

DISCUSSION

There are scarce data regarding the potential toxic effects of organochlorine (OC) and organophosphorus (OP) pesticides on the immune system especially in infants and children. In addition, controversial results render them inadequate to raise a precise conclusion regarding their immunotoxicity (Corsini et al., 2008; Fukuyama et al. 2010; Winans et al., 2011).

Despite the ability of several pesticides to increase the levels of autoantibodies, few studies have evaluated their possible role as risk factors for autoimmune diseases (Corsini et al., 2008). To the best of our knowledge, this is the first study aiming to assess the potential immunotoxic effects of some pesticides in relation to type 1 diabetes in a group of Egyptian children.

In the present work, lindane; o.p-DDD; p.p-DDE; endrin; o.p.DDT and p.pDDA were the detected organochlorine pesticides while malathion; chlorpyrifos-methyl and profenofos were the detected organophosphorus pesticides in the studied diabetic children. Results showed that lindane was the most common (70.7 %) followed by malathion (65.3%). Both compounds had the highest odds ratio (≥ 2) indicating a probable increased risk of occurrence of type 1 diabetes in the exposed children.

Regarding the investigated immunological markers, the current results revealed that diabetic children had higher WBC counts and lymphocyte % than the control group. This was possibly due to the direct effect of pesticides on humoral and cell-mediated immune responses as previously stated by Karmaus et al. (2005) and Li (2007).

It was also postulated that there is an association between total peripheral WBC count (a non-specific marker of inflammation) and diabetes risk. There is a considerable uncertainty about the direction of causality regarding the relationship between diabetes and inflammation despite that the latter is thought to promote beta-cell death (Hotamisligil, 2006).

The present findings showed marked differences between diabetic patients and control group regarding the percentages of various lymphocyte subpopulations. In diabetic children, a highly significant correlation was seen in relation to lindane exposure ($P < 0.05$) concerning the percentages of $CD4^+$ (T helper cells) as well as $CD4^+/CD8^+$ ratio.

The lower $CD4^+/CD8^+$ reflects the alteration in the amount of circulating cells

with decreased CD4+ and increased CD8+ expression indicating immunosuppression, which may point to the ongoing process of B-cell destruction. Another explanation is the presence of defects in soluble cytokines and membrane-associated molecules in diabetic children which affect the stimulation of CD4+. Moreover, T1DM is believed to result from the selective autoimmune destruction of pancreatic islet _ insulin-producing Langerhans cells which is primarily mediated by the cytotoxic (CD8+) T cells (Dotta et al., 2007; Cernea and Herold, 2010).

Likewise, Dewailly et al. (2000) reported that CD4+ lymphocytes were lower in children exposed to OC especially DDE compared to control subjects. Consistently, Nagayama et al. (2007) proved a similar alteration in the CD4+/CD8+ ratio in Japanese infants and that exposure to HCE and chlordane significantly increased the percentages of CD8+ and CD3+ T cells respectively.

Concerning lindane, there is a paucity of literature regarding its immunotoxic effects in humans. Seth et al. (2005) reported that lindane impaired the immunocompetence and caused an overall decrease in humoral, cell-mediated, and indirect immune responses. The current observations may be due to the immunotoxic effect of lindane on the immunoregulatory cytokines levels (interleukins: IL2, IL4, tumour necrosis factor: TNF-γ and interferon gamma: INF-γ) and subsequently, these cytokines affect the proliferation of T cell lymphocytes.

Alternatively, Glynn et al. (2008) demonstrated that postnatal exposure to organochlorines had no significant association with numbers and percentages of WBCs and lymphocyte subsets except among infants with the highest post-natal p,p-DDE exposure who showed an increased percentage of lymphocytes. This could be due to different studied subjects and alternative pesticides detected.

In the current work, assessment of T cells with HLA-DR activation marker in diabetic children revealed an increased percentage and a significant association of diabetes in relation to pesticides.

In agreement with this finding, Nagayama et al. (2007) assessed the immunological changes induced in Japanese infants due to exposure to organochlorine compounds. They reported an increased expression of CD3+ HLA-DR+ T cells. It is known that the primary function of HLA-DR is to present foreign peptide antigens to the immune system to elicit or suppress T-helper cell responses leading to production of antibodies against those peptide antigens. HLA-DR+ is found in antigen presenting cells (macrophages, B-cells and dendritic cells). It was proved that the

increased abundance of DR 'antigen' on the cell surface in insulin dependent diabetes mellitus (IDDM) patients could occur in response to immune stimulation (Kaaba and Al-Harbi, 1995; Dotta et al., 2007) and therefore, DR is a marker for immune enhancement that would occur as a response to various environmental triggers including pesticides.

The present results show a significant correlation between exposure to malathion and the expression of CD4+ (helper T cells) in the studied diabetic group. Moreover, a significant association is also found concerning CD20+ B cells expression.

On the contrary, Thrasher et al. (2002) found that there was no effect of organophosphorus pesticides on B cell population in humans. This may be due to different studied OP compounds and subjects. Some reports indicated that OP compounds can affect the immune system in humans through alteration of the abundance of some leukocyte subpopulations, the complement function, cell proliferation, cytokine secretion and surface marker expression (Li, 2007).

The present findings are contradictory to Esquivel-Sentíes et al. (2010) who proved that there was decreased proliferation of both total T lymphocytes (CD3+ cells) and CD4+T cells, as a result of reduced secretion of IL-2, IFN-γ and IL-10 .

In another study conducted by Duramad et al. (2006), they found that OP chlorpyrifos and its metabolite modulate the expression of IFN-γ and IL-4, T-helper (Th1 and Th2) signature cytokines which reflect the increased percentage of CD4+T cells.

More or less similar, Steerenberg et al. (2008) examined the prolonged low-dose exposure of mixtures of pesticides on hematological parameters and components of the immune defense in exposed humans. They found that the CD8+ subpopulation was increased which could be explained by immunomodulatory effects of pesticides on cytokines which in turn affect the expression of CD8+.

On the other hand, assessment of CD16+ T cells in the studied diabetic children seemed more obvious as there was a decreased percentage and a statistically significant negative correlation (P =0.02).

This is nearly consistent with previous data which stated that exposure to OP (Chlorpyrifos) significantly inhibits the activities of natural killer (NK) cells by either impairing the granule exocytosis pathway responsible for the release of cytolytic granules from NK cells or induction of apoptosis in the immune cells (Li and Kawada, 2006).

In conclusion, the present work re-

vealed that some pesticides had a significant association with the immune response of different lymphocyte subsets in exposed diabetic children. The present results seemed partly in agreement with some of the previously mentioned studies, despite the difference in chemical compounds that exerted such effects. Studying the direct causal relationship is not within the scope of this work. However, the detected immune modulation may be of clinical significance and indicates that those environmental pollutants might play a role in raising the incidence of sensitization to different antigens with earlier onset of autoimmune diseases such as T1DM.

RECOMMENDATIONS

Generating precise exposure-response data concerning the immunotoxicity of pesticides necessitates checking other confounding factors such as genetic susceptibility, combined exposure to various xenobiotics, diet and other lifestyle factors that could affect the incidence of T1DM especially in the highly vulnerable groups i.e. infants and children. Hence, it is recommended to perform studies to find out the direct causal relationship of various pesticides regarding initiation or facilitation of autoimmune diseases.

In the meantime, the prevention of further environmental contamination is essential, in order to minimize the exposure to these toxic compounds. Follow-up immunological analysis of children to adulthood is also suggested.

Table (1): Concentrations of pesticides residues (ng / ml) in the serum of the studied groups and their odds ratios (OR).

Pesticides residues detected	**Control (n = 35)**		**Patients (n = 75)**		**p**	**OR**	
Organochlorines (OC)	**n (%)**	**Median (Min – Max)**	**n (%)**	**Median (Min –Max)**		**(95 % Confidence Interval)**	
Lindane	19 (54.3%)	< LOD	53 (70.7%)	0.54 (0.00 – 0.87)	0.00*	2.02 (0.88-4.65)	
Endrin	*0*	< LOD	8 (10.7%)	0.90 (0.88 – 0.96)	0.00*	1.52 (1.32-1.75)	
o.p.DDD	*0*	< LOD	16 (21.3%)	0.75 (0.16 – 4.3)	0.00*	1.59 (1.36-1.86)	
p.p.DDE	*0*	< LOD	16 (21.3%)	0.28 (0.1 – 0.97)	0.00*	1.59 (1.36-1.86)	
o.p.DDT	9 (25.7%)	< LOD	6 (8%)	0.00 (0.01 – 0.61)	0.00*	0.25 (0.08-0.77)	
p.p.DDA	*0*	< LOD	4 (5.3%)	1.07 (0.51 – 1.64)	0.00*	1.49 (1.30-1.70)	
Organo-phosphates (OP)							
Malathion	11 (31.4%)	0.03 (0.02 – 0.05)	49 (65.3%)	0.61 (0.11-1.01)	0.00*	4.11	(1.74-9.69)
Profenofos	6 (17.1%)	0.03 (0.03 – 0.04)	2 (2.7%)	0.47 (0.47 – 0.47)	0.03*	0.13	(0.02-0.69)
Chlorpyrifos-Methyl	12 (34.3%)	0.03 (0.01 – 0.04)	6 (8%)	0.00 (0.00 – 0.72)	0.25	0.16	(0.05-0.49)

Lindane: (hexachlorocyclohexane isomer: γ-HCH); **o,p'-DDT**: 1-(o-chlorophenyl) -1- (p-chlorophenyl)-2,2,2 trichloroethane; **p,p'-DDE** (1,1-dichloro-2,2-bis (p.chlorophenyl) ethylene; **o,p'-DDD**: 1- (o-chlorophenyl)-1-(p-chlorophenyl) -2,2-dichloroethane; **p.p DDA**: " 2,2-bis-4-chlorophenyl acetic acid"; **LOD**: limit of detection; **Min:** minimum; **Max**: maximum. ***p is significant if < 0.05.**

Table (2): The investigated immune markers (mean ± SD) of the studied groups (n=110).

Immune Markers	Control group (n = 35)	Studied patients (n = 75)	t	P
	Mean ± SD	Mean ± SD		
WBC x10^9/L	9.11 ± 0.94	11.38 ±1.29	9.27	0.00*
Lymphocytes %	45.34 ± 5.56	60.22 ± 5.92	12.51	0.00*
ALC	4.17 ± 0.86	6.88 ± 1.04	13.38	0.00*
CD 3%	67.94 ± 6.33	75.22 ± 6.21	5.68	0.00*
CD4%	40.42 ± 4.46	33.54 ± 2.58	-10.20-	0.00*
CD8%	26.14 ± 5.34	34.22 ± 4.29	8.49	0.00*
CD4/8 ratio	1.58 ± 0 .32	1.03 ± 0.20	-10.65-	0.00*
CD20%	20.57 ± 1.61	20.52 ± 5.48	-.05-	0.95
CD16%	11.22 ± 2.07	10.80 ± 0.75	-0.43-	0.003*
HLADR%	22.62 ± 3.21	25.54 ± 3.01	4.51	0.000*

WBC: white blood cell; **ALC**: absolute lymphocytic count, **CD**: cluster of differentiation**; HLADR:** human leukocytic antigen (major histocompatibility complex class II)**. *P < 0.05 is significant.**

Table (3): Correlation between detected pesticides residues with highest odds ratio and different immune markers of the studied groups (n = 110).

Immune Markers	Lindane		Malathion	
	Control	**Diabetic**	**Control**	**Diabetic**
WBC (x10^9/L)				
r	0.24	0.13	0.95	0.13
P	0.31	0.34	0.431	0.34
Lymphocytes %				
r	0.36	-0.19	-0.14	0.15
P	0.12	0.15	0.66	0.27
ALC				
r	0.32	0.01	0.21	0.21
P	0.17	0.91	0.52	0.13
CD 3%				
r	-0.25	-0.09	0.57	-0.22
P	0.29	0.50	0.06	0.11
CD4%				
r	0.20	-0.30	-0.640	0.50
P	0.41	0.02*	0.134	0.00*
CD8%				
r	0.25	-0.19	1.000	0.05
P	0.28	0.16	0.100	0.70
CD4/8 ratio				
r	0.21	-0.52	-0.923	0.28
P	0.38	0.00*	0.120	0.04*
CD20%				
r	0.39	-0.16	-0.113	0.30
P	0.09	0.22	0.742	0.03*
CD16%				
r	0.41	0.01	-0.992	0.33
P	0.07	0.93	0.087	0.02*
HLADR%				
r	0.02	-0.39	-0.813	0.51
P	0.91	0.003*	0.092	0.00*
Summary of significant immnodulatory effects in relation to pesticides	- ***In control group***: No significant correlation. ***-In diabetic group***: CD4*; CD4/8*; HLADR*		- ***In control group***: No significant correlation. ***-In diabetic group***: CD4*; CD4/8*; CD20*; CD16*; HLADR*	

WBC: white blood cell; **ALC**: absolute lymphocytic count, **CD**: cluster of differentiation**; HLADR:** human leukocytic antigen (major histocompatibility complex class II). ***P < 0.05 is significant.**

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التأثيرات السمية لبعض المبيدات على المناعة في الأطفال المصريين مرضى السكرى

المشتركون فى البحث

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كلية الطب – جامعة المنصورة

مرض السكري من النوع الأول (T1DM) هو اضطراب المناعة الذاتية المزمنة والتي يمكن أن يكون سببها التعرض لمختلف الملوثات البيئية وتحفيز حدوث هذا المرض خاصة في الأفراد الأكثر عرضة وراثيا. وتم إلقاء الضوء على العلاقة المحتملة بين امكانية حدوث خلل فى الجهاز المناعى بسبب التعرض للمبيدات السامة خصوصا فى الأطفال.

تهدف هذه الدراسة الى تقييم استجابة جهاز المناعة في مجموعة من الأطفال مرضى السكري وعلاقتها بالتعرض لبعض المبيدات الحشرية. وقد شملت الدراسة مائة وعشرة طفل تراوحت أعمارهم بين ٢ , ١و ١٠ سنوات، تضم المجموعة الضابطة ٣٥ طفلا ، في حين اشتملت مجموعة الدراسة على ٧٥ طفلا تم تشخيصهم حديثا كمرضى السكري من النوع الأول. وتم أخذ عينة دم من كل طفل لإجراء تحليل لبقايا المبيدات السامة بالدم باستخدام جهاز التحليل الكروماتوجرافى (GC). كذلك تم عمل بعض التحاليل المناعية بالدم. وقد أظهرت النتائج أن بعض المبيدات (الليندان والملاثيون) التي كانت ذات أعلى معامل خطورة فى ارتباطها بحدوث مرض السكرى لها أيضا تأثير ذو دلالة احصائية على التغيرات التى تحدث فى الخلايا الليمفاوية في الأطفال مرضى السكري مقارنة بالأصحاء.

ونخلص من هذه الدراسة إلى أن المبيدات يمكن أن تلعب دورا محتملا بشأن زيادة حالات مرض السكرى في الأطفال لما لها من تأثير على جهاز المناعة. وننصح بمزيد من الدراسات السكانية الكبيرة لإثبات العلاقة السببية المباشرة بين المبيدات المختلفة والأمراض المناعية التى قد يزداد حدوثها جراء التعرض لتلك الملوثات البيئية.