Cod: 8.1005

TCDD AFFECTS RESPONSE TO TETANUS TOXOID VACCINATION

F. Cappellini[1], M. Cazzaniga[1], C. Sarto[1], S. Signorini[1], G. Limonta[1], L.L. Needham[2], D.G. Patterson[2], P. Brambilla[1], P. Mocarelli[1]

[1]*University Department of Laboratory Medicine, University Milano-Bicocca, Hospital of Desio, Desio (MB), Italy*

[2]*Centers for Disease Control and Prevention, Division of Laboratory Sciences, Atlanta, GA, USA*

INTRODUCTION

Polychlorinated compounds, such as dibenzo-p-dioxins and dibenzofurans, are persistent worldwide contaminants and among them, 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD or dioxin), produced by various industrial chemical reactions and combustion processes is one of the most potent toxic chemicals. An explosion which occurred in a chemical factory near Seveso (Italy) in 1976 probably released more than 30 kg of dioxin into the environment.

A potential sensitive target of TCDD is the immune system. Following exposure to dioxin, laboratory animals showed decreased resistance to viral or parasitic infections and general immunosuppression (1). However, following TCDD exposure and tetanus immunization, nonhuman primates (Callithrix jacchus) exhibited a prolonged in vitro proliferative response to recall antigen (2). In humans TCDD effects on the immune system are not entirely clear (3).

In the period from 1992 to 1994, we studied levels of circulating anti-tetanus toxoid specific IgG in subjects exposed in 1976 to TCDD and in matched unexposed controls.

MATERIALS AND METHODS

The study population consisted of 44 exposed subjects and 42 unexposed controls who were 2-17 years of age in 1976 at time of TCDD release; all of them received their last booster of tetanus toxoid between 1979 and 1994. Subjects were divided into two groups according to the period of the last booster injection: one group of subjects who received the booster 5 to 13 years prior to the IgG measurements (exposed males, n=12; non-exposed males, n=14; exposed females, n=10; non-exposed females, n=10) and the other one up to 5 years prior (exposed males, n=12; non-exposed males, n=10; exposed females, n=10; non-exposed females, n=8;).

The anti-tetanus toxoid IgG concentrations were measured by an Enzyme-Linked Immunosorbent Assay (ELISA, Genzyme Virotech, Germany) and TCDD was estimated by high-resolution mass spectrometry in serum samples obtained both in 1976 and in the same period of anti-tetanus toxoid IgG evaluations, 1992-1994.

RESULTS AND DISCUSSION

TCDD concentrations in the 1976 serum samples ranged from 54 parts-per-trillion (ppt) to 26,400 ppt (median: 704 ppt) in exposed males and from 30 ppt to 56,400 ppt (median: 2,500 ppt) in exposed females.

Among subjects who had the booster injection between 5 and 13 years prior to the IgG measurement, the 12 exposed men had a statistically different ($p<0.0001$) mean value of anti-tetanus toxoid IgG (2.23 mIU/mL) compared to 14 non-exposed controls (mean=0.53 mIU/mL), figure 1. In this group of exposed males, the anti-tetanus toxoid IgG serum concentrations positively correlated ($p=0.08$) with TCDD measured in 1976 (figure 2) but not with 1992-1994 TCDD.

Among subjects with booster up to 5 years before IgG measurements, the exposed men had a mean value of anti-tetanus toxoid IgG (3.35 mIU/mL) similar to that obtained in 10 non-exposed control males (mean=3.06 mIU/mL).

The persistence of high levels of IgGs against tetanus observed in men was not observed in females, which did not show significant difference between exposed and non-exposed females in both groups according to the period of the last booster.

In conclusion, we found that TCDD exposed males, belonging to the group of subjects who received the tetanus toxoid booster injection 5-13 years prior the IgG measurement, had higher levels of serum antibodies directed to tetanus toxoid respect to non-exposed. Moreover, in the exposed males the IgG values correlated positively with TCDD concentration at exposure in 1976 and not with that at the time of IgG evaluation.

In humans elevated exposure to perfluorinated compounds were associated with reduced humoral immune response to childhood immunizations (4) while TCDD exposure effects in humans are less clear. Our results are consistent with data obtained in nonhuman primates after toxoid vaccination suggesting a stimulating effect of TCDD on immune system (2) while many animal studies suggest a suppressive effect. Our findings may support the idea, as proposed by Dr. Kerkvliet, about a new paradigm for TCDD toxicity on the immune system, moving from a "simple" mechanism of a general suppression of immune functions to an inappropriate activation of different immune cells by TCDD exposure (5).

References:

1. Kerkvliet, N.I. (2012) Toxicol Pathol 40(2):138-42.
2. Neubert, R., Helge, H., Neubert, D. (1995) Life Sci 56(6):437-44.
3. Marshall N.B., Kerkvliet, N.I. (2010) Ann N Y Acad Sci 1183:25–37.
4. Grandjean, P., Andersen, E.W., Budtz-Jørgensen, E., Nielsen, F., Mølbak, K., Weihe, P., Heilmann, C. (2012) Jama 307(4):391-7.
5. Kerkvliet, N.I. (2002) Int Immunopharmacol 2(2-3):277-91.

Figure 1
Serum anti-tetanus toxoid IgG values in TCDD exposed and non-exposed males

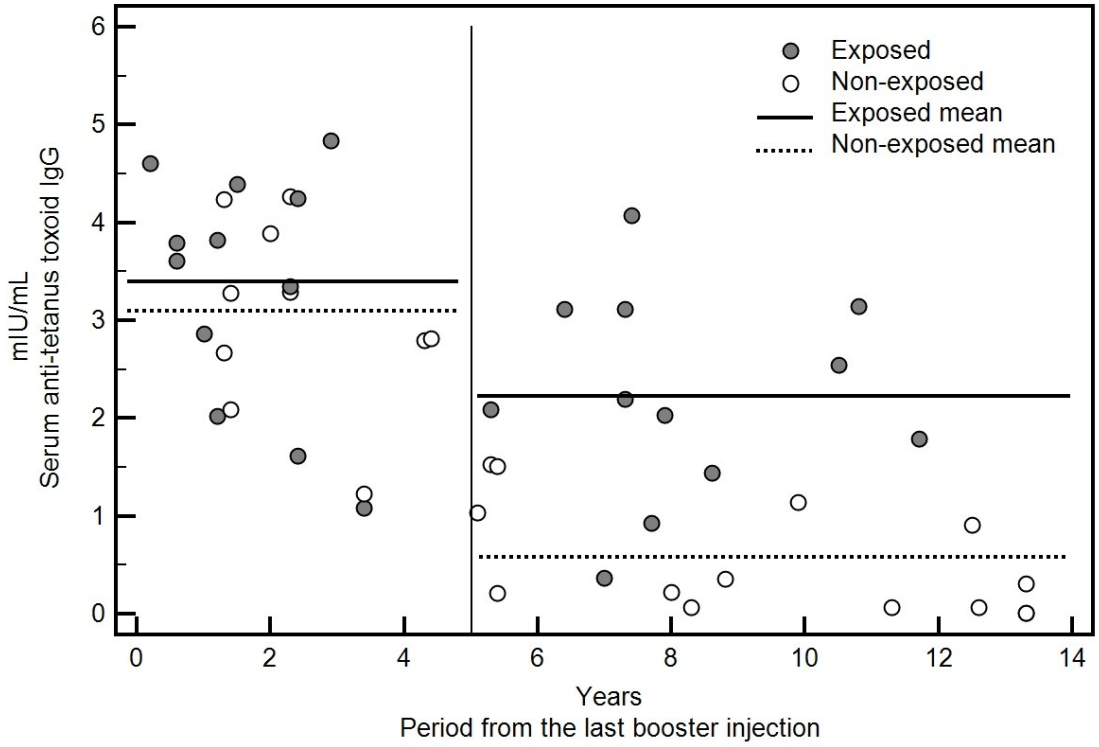

Figure 2
Serum anti-tetanus toxoid IgG values and 1976 TCDD:
regression analysis in 12 exposed males