IMMUNE RESPONSE TO EXPOSURE TO OCCUPATIONAL AND ENVIRONMENTAL AGENTS

Recognition that xenobiotics can impair the function of the immune system has led to progress in immunotoxicology over the last two decades. Exposure to immunotoxic chemicals in the environment, however, may be expected to result in more subtle forms of immunosuppression that may be difficult to detect, leading to increased incidences of infections such as influenza and common cold. Studies on experimental animals and humans have shown that many environmental chemicals suppress the immune response. Immunotoxic xenobiotics are not restricted to a particular chemical class. Compounds that adversely affect the immune system are found among drugs, pesticides, solvents, halogenated and aromatic hydrocarbons, metals, etc.

Therapeutic administration of immunostimulating agents can have adverse effects, and a few environmental chemicals that have immunostimulating properties (beryllium, silica, hexachlorobenzene) can have clinical consequences. Reports on the assessment of immunotoxicity in humans exposed to various agents as a part of occupational exposure are relatively scarce. Apart from various routine toxicological evaluations this is an important parameter that can provide information on body responses which may be responsible for a sequence of reactions leading to pathogenesis. Some of these parameters can be used as a biological marker for the early detection of disease due to occupational exposure to the agent.

The National Institute of Occupational Health (NIOH), Ahmedabad has carried out several human and experimental studies on immunological changes in various occupational exposures including pesticides such as BHC, DDT, cyfluthrin, malathion and metals such as cadmium and mercury, dust like asbestos, cotton and silica and chemicals such as methyl isocyanate (MIC). This write-up gives an overview of studies undertaken to find out the immunotoxicological changes due to exposure to occupational agents as well as involvement of the immune system as a response to these agents.

DUST DISEASES

The term pneumoconiosis which simply means dusty lungs was coined by zenker in 1866. Pneumoconiosis was defined at the IVth International Conference on Pneumoconiosis in 1971 as the accumulation of the dust in the lungs and the tissue reactions to its presence. The dust was defined as an aerosol composed of solid inanimate particles. The occupational lung disorders according to the biological properties of the material inhaled were grouped into four main types viz. (i) Disorders caused due to exposure to mineral dust (coal dust, silica, talc, asbestos, kaolin, iron, etc); (ii) Disorders caused due to exposure to gases and fumes (ammonia, chlorine, phosgene, sulphur dioxide, oxides of nitrogen and fumes of various metals); (iii) Disorders caused due to exposure to organic dust (mouldy hay, cotton dust, sugarcane dust, maple bark dust, etc.); and (iv) Pulmonary and pleural malignancy caused by asbestos exposure leading to pleural mesothelioma.
**Occupational Exposure to Silica**

Silica is one of the most fibrogenic material found in nature. The reason for this fibrogenic property remains largely unknown. There are various theories, which explain the strong fibrogenic properties of silica, but none of them seems to provide a complete explanation.

(i) Theory of Peizo-electric effect: This theory suggests that minute electrical currents caused by mechanical stress in the quartz crystal damage the tissue.

(ii) Solubility theory: This theory postulates the dissolution of silica into the tissue fluids producing silicic acid which causes fibrosis.

(iii) Phospholipid theory: According to this theory death of macrophage due to silica results in release of phospholipids that are fibrogenic.

(iv) Immunological theory: This theory suggests there are three possible ways in which free silica particles might cause immunological reaction – silica acting as an antigen, by producing an auto antigen or by acting as an adjuvant.

The other theories, which have gained importance, are fibrogenic factor theory of Heppleston and Styles, wherein macrophage after ingestion of quartz particles release macrophase fibrogenic factor which stimulates the fibroblast to increase the production of collagen. This macrophase fibrogenic factor has been further confirmed by other workers. The studies reported by NIOH scientists indicate increased levels of immunoglobulins supporting the hypothesis that there is humoral immune dysfunction in silicosis. Similar observations have also been made by other workers suggesting polyclonal activation of B cells. This study also demonstrated the lack of correlation between immunoglobulin level and severity of silicosis, although a rising trend of IgG and IgM associated with the duration of exposure was observed in the dust exposed group with conglomerate silicosis. No definite factor is known which acts as a stimulus for elevation of immunoglobulins in silicosis. Miners and tunnelers exposed to free silica dust have been found with significantly elevated levels of IgG and IgA and this was more evident in workers with simple silicosis. Workers with conglomerate silicosis have 15 years of exposure, and higher levels of IgG and IgM are seen in radiologically proven conglomerate silicosis.

**Occupational Exposure to Asbestos**

Asbestos includes a number of naturally occurring silicates with the common property of great resistance to destruction by physical or chemical means. Due to its strength, and resistance to fire, acid and alkali asbestos has become almost indispensable in modern industry.

Asbestosis is a diffused interstitial fibrosis of the lung resulting from exposure to asbestos dust. Fibrosis occurs as a result of a series of cellular events following the exposure involving alveolar macrophages and lung fibroblasts. The role of growth factors released by other cells which control fibroblast proliferation during accumulation of dust in the respiratory bronchioles has been emphasized. Involvement of the immunological system in the etiopathogenesis of pneumoconiosis has been strongly suspected. There are a number of direct and indirect evidences showing increase in the prevalence of antinuclear antibodies, rheumatoid factor and immune complexes and increased immunoglobulins suggesting that multiple factors play a role in the pathogenesis of asbestosis. Increase in IgA levels was of greater significance as it reflects the involvement of local antibody production in the pulmonary tissue. Generation of IgA is more dependent on T helper cells than IgG or IgM. Presence of antinuclear factor (ANF) in asbestosis has been reported by earlier workers. Asbestos fibre cause tissue injury and some component of the asbestos fibres probably reacts with the nuclear proteins making these proteins new antigen, to which further antibodies are produced. Therefore autoimmunity develops in this fibrotic lung disease. Another possible explanation for positivity of ANF is that, asbestos fibres interfere with T suppressor cell regulation of antibody production by B cells. Therefore, due to deregulation of B cells abnormal antibodies are produced to nuclear antigens by the mature plasma cells. The presence of circulating immune complexes (CICs) in workers exposed to asbestos has been reported. Significant increases of CICs of IgM and CICs of IgG were found in workers with asbestosis and those exposed to asbestos but without asbestosis. These observations suggest that the immune complexes possibly play a role in the pathogenesis of asbestosis. Increase in the CICs and also in complement can initiate the process which can ultimately lead to fibrotic changes in the lungs of workers exposed to asbestos. Incomplete clearance of CICs can result in persistent activation of complement; also deposition of CICs of IgA can lead to fibrogenic changes by triggering an alternative pathway.
Pneumoconiosis due to Other Silicates

Besides asbestos other silicates which are capable of causing occupational hazards include talc, sericite, sillimanite and glass wool, all of which occur in fibrous form and silicates like mica, kaolin and fuller’s earth which occur in the non-fibrous form. Cement, a complex compound of calcium aluminates and calcium silicate, does not cause pneumoconiosis unless it contains over 2% free silica as contaminant.

Cotton Dust Exposure

Byssinosis is a chronic respiratory disease of cotton, flax and soft hemp workers. The workers exposed to cotton dust in textile mills showed significant rise in IgG with or without byssinosis; IgA and IgM increased (non significantly) only in byssinosis. Similar changes in immunoglobulins have also been described by other workers.

Environmental and Occupational Chemicals including Pesticides

So far only a few environmental chemicals have been shown to possess immunostimulating properties, eg hexachlorobenzene and selenium. There have been no reports of clinical reactions to such chemicals that are similar to the adverse effect seen with immunostimulating drugs.

In an unsubstantiated study, a cluster of patients of Hodgkin’s disease reported in a small town in Michigan, USA was ascribed to chronic immune stimulation by mitogenic substances in the environment. Immunological studies of the family members of the index cases revealed a large number of individuals with altered ratios of T lymphocyte subpopulations, auto antibodies, infections, recurrent rashes and NK cell function. A report of a four year study of workers engaged in the manufacture of benzidine (also occupational exposure in benzidine based dye industry) suggested that the individuals with depressed cell mediated immunity has precancerous conditions and subsequent neoplasm. The workers with normal immunological responses did not show neoplastic disease.

Air Pollutants

Oxidant gases have been associated with an increased prevalence of respiratory infections particularly bacterial and their potential immune effects, but the data are less convincing than those of animal studies. The association between air pollution in industrialized areas and altered health status has been well established in epidemiological studies. A number of studies have linked exposure to air pollutants (ozone, nitrogen dioxide, sulphur dioxide, environmental tobacco smoke) with an increased incidence, severity or duration of symptoms associated with respiratory infections.

Polycyclic Aromatic Hydrocarbons

Most polycyclic aromatic hydrocarbons (PAHs) have carcinogenic potential. Carcinogenic chemicals also have potent immunosuppressive properties, whereas those, which are not, lack marked immunotoxic effects. Suppression of humoral immunity has been observed frequently after exposure to a number of PAHs including benzo(a)pyrene, DMBA and 3-methylcolenthrine. PAHs also suppress cell mediated immunity. T lymphocyte cytotoxicity and mixed lymphocyte responsiveness were found to be impaired by most PAHs. Various mechanisms have been suggested for the immunosuppression due to PAHs. The effect may be due to parent compound or its metabolites, altered interleukin levels, a direct effect on transmembrane signaling or alteration in intracellular calcium mobilization.

Solvents

Exposure to benzene is associated with myelotoxicity and a strong correlation between lymphocytopaenia and abnormal immunological parameters. The hydroquinone a metabolite of benzene has potential to block the final maturation stages of B cell differentiation. The mechanism of benzene induced immunosuppression is still unclear. Benzene has potential to alter cytoskeletal development through inhibition of microtubule assembly. The polyhydroxy metabolite of benzene binds to sulphhydryl groups on the proteins, which are necessary for the integrity and polymerization of microtubules. This effect may alter self membrane fluidity, which explains the sub lethal effect of benzene on lymphocyte function.

Pesticides

Pesticide exposure also invokes immune response. Individuals exposed to serum PCB concentrations up to 30 mg/l showed lowered numbers of T cells 5 weeks after the exposure which returned to normal values within 7 weeks after exposure. The immune status of subjects exposed to tetrachlorodibenzodioxin (TCDD) during the 1976 accident at Saveso, Italy have also been studied.
An evaluation of 44 exposed children (20 with chloracne) showed no overt changes in the immune status.

DDT and BHC are the most commonly used insecticides in India. These chemicals have been shown to have carcinogenic potential in experimental animals. These insecticides accumulate in the body due to their lipophilic nature. Serum hexachlorocyclohexane residues have been reported in workers manufacturing HCH. The immunological profile in workers occupationally exposed to pesticides has also been reported.

Samples with significantly higher levels of serum HCH showed presence of CICs of IgG in 25% samples and CICs of IgM in 51% samples. CICs of complements were not detected. The immunoglobulins showed elevated levels though not uniformly, in different exposed groups in the same study. The group with the highest exposure showed increase in IgM while IgG and IgA increases were observed in the comparatively less exposed group. IgM increase was significantly correlated with α serum globulins. Since immune complexes are implicated in the pathogenesis of neoplastic diseases their presence in the serum of workers occupationally exposed to HCH during manufacturing is important.

Studies on the occupational exposure to pesticides (cyfluthrin, malathion, DDT) during spraying operation and the immune profile of exposed workers have shown increased levels of IgG (malathion exposure). On exposure to cyfluthrin increase in IgG levels was observed with increased duration of exposure. All the groups (cyfluthrin, malathion, DDT) showed increase in CICs of IgG, however, no parallel increase in the C3 and C4 complements were observed. Normally CICs activate the complement pathways therefore increased complements are expected.

**Halogenated Aromatic Hydrocarbons**

Apart from the occupational exposures to these compounds, human exposures to halogenated aromatic hydrocarbons have occurred in a number of chemical accidents. In Taiwan more than 2000 people were exposed to rice oil contaminated with PCB and polychlorinated dibenzofurans. Examination of the immune status one year after exposure showed, decreased concentrations of serum IgM and IgA but not IgG in addition to decreased number of circulating T helper cells.

A similar incident occurred in Japan in 1978 resulting in Yusho syndrome. The immune system was assumed to be affected because of an increased frequency of respiratory infection and lowered serum IgM and IgA concentrations.

Another incidence of intoxication with PCB and polychlorinated dibenzofurans occurred after exposure to contamination with soot of fires in electrical equipment.

**Occupational Exposure to Heavy Metals**

Heavy metals including lead, cadmium and mercury are capable of altering the immune response in laboratory animals. Reported evidence suggests that human exposure to metals may result in immune system defects. Workers in the lead industry with blood lead levels of 52 µg/100ml have demonstrated decreased levels of serum complement as well as decreased levels of secretory IgA. The cationic heavy metals like mercury, gold and lead have been associated with immune complex diseases in humans. There is more than one mechanism operable in immunotoxicity due to metals. Defect in B cell function is suggested to reside at the level of plasma cell development. Impaired accessory cell function or deficient complement system is also implicated.

Defect in B cell function is suggested to reside at the level of plasma cell development. Impaired accessory cell function or deficient complement system is also implicated. Lead as well as cadmium are sulphhydryl alkalyting agents with high binding affinity for cellular and sulphhydryl groups. They modulate membrane bound thiols and thus alter the lymphocyte function. The augmentation of T and B cell responsiveness stated as above could precipitate autoimmunity. Metals have been implicated in influencing autoimmunity.

**Mercury**

Significantly decreased levels of serum IgG and IgA but not IgM, IgD or IgE were observed in workers occupationally exposed to metallic mercury vapours chronically. Inorganic mercury exposure did not produce immunologic disturbances in the exposed workers which implies that the immune system of most exposed individuals was insensitive to low levels of inorganic mercury or tolerates it, nevertheless not all individuals were insensitive to low dose mercury exposure. The dose response and the dose effect estimations in immunotoxicology are complicated and it is well known from studies on animal models, that generally restricted factors predispose a person to the development of mercury induced autoimmune phenomena. Study of chronic exposure to mercury on the basis of mercury levels in urine or blood, is also difficult. In a study on workers exposed to inorganic mercury in a chloralkali plant, no correlation was observed between blood mercury levels.
and immunoglobulins among control, moderately exposed and heavily exposed groups. However, when the groups were made on the basis of CNS or oral morbidity, a significant positive correlation was seen with increased blood or urine mercury and immunoglobulins among the groups. These CNS or oral morbidity groups also showed significant increase in CICs of IgA and CICs of IgG. Few samples were also CRP positive.

Beryllium

Beryllium induces a variety of diseases including granulomatous lungs (chronic beryllium disease), and skin conditions. In these granulomatous reactions lymphocytes respond to beryllium salts. The major lymphocyte population consists of the CD4 cells. The T cell response to beryllium is IL2 dependent. The antigen has not been identified but may be a beryllium protein complex. There appears to be a genetic predisposition as most patients with beryllium lung disease share a particular HLA-Dp allele (HLA-DpB1).

CONCLUSIONS

Immunotoxicology is a study of interactions of chemicals, metals, drugs, etc. with the immune system. The prime concern is to assess the importance of these interactions with regard to human health. The toxic response may occur when the immune system is the target of chemicals resulting in altered immune function; this in turn can result in decreased resistance to infection, certain forms of neoplasia, or immune dysregulation or stimulation which exacerbates allergy or autoimmunity. Alternate toxicity may arise when the immune system responds to the antigenic specificity of the chemical as part of a specific immune response (allergy or autoimmunity). Certain drugs induce autoimmunity.

A number of substances affect immunological parameters; these include halogenated hydrocarbons, polychlorinated dibenzoaradioxins and polychlorinated dibenzofurans; pesticides (DDT, HCH, cyfluthrin, malathion, etc.); organic solvents; asbestos; silica and metals like lead, cadmium, mercury. Oxidant air pollutants like sulphur dioxide, nitrogen dioxide, ozone and air-borne dust particles may affect immune function.

The detection of immune changes on exposure to immunotoxic agents is more complicated and difficult in humans than in experimental animals. The studies reported have several constrains considering confounding factors such as age, sex, race, gender, co-existence of disease, food habits, tobacco smoking, chewing, etc. The assessment of the immune changes due to occupational exposure may need study of the profile of the individual or population. Though the studies reported so far are on only a few parameters, they are important due to the results obtained. The overall objectives of such studies are to know if immune system is affected, the immunopathogenesis of the disease condition, dose response relationship, qualitative or quantitative estimate of adverse outcome and to estimate the health risk. The ultimate purpose of risk assessment is to protect human health, although there are difficulties in establishing a quantitative relationship between immunotoxicological data and risk assessment.

References


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