

IMMUNOLOGICAL SIGNIFICANCE OF NEGATIVE MANTOUX TEST IN TUBERCULOUS PATIENTS

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Resistance to infection by micro-organism is based on non-specific and specific immunity. Non-specific immunity makes one innately susceptible or resistant to certain infections. Some of these factors are low pH of skin, lysozyme-bactericidal enzyme, mucous secretion in lung and phagocytosis. Specific immunity against micro-organism is acquired and operates by cell mediated reaction and humoral antibody synthesis. Specific immunity operates in co-operation with non-specific immunity and increases its effectiveness.

Both cellular and humoral systems are essential for protection of man. The incidence of diseases is higher in both genetic and acquired humoral and cellular deficiencies. For example, immune suppression by X-ray, corticosteroid and cytotoxic drugs, in lymphoproliferative disorders like lymphocytic leukemia and myeloma, malnutrition and certain viral infection like measles.

Immune deficiency is clinically recognisable. In C.M.I, deficient infant immune responses are absent just after birth. They can deal with common bacterial infection. Infection by Herpes Zoster indicates deficient C.M.I. These children get over-whelmed by vaccinia and measles virus and B.C.G. if given by mistake. Humoral immune deficiency is recognisable at the age of 4 months, when the protection by mother IgG disappears. Presence of Candida infection indicates humoral deficiency. These children are prone to repeated infection by pyogenic organisms whereas measles and small pox are readily brought under control.

It is well known that malnutrition, corticosteroid therapy, measles and Hodgkin's disease predispose to tuberculosis. All these conditions lead to deficient immune response.

The patients with deficient C.M.I, are hyporeactors or non-reactors to skin test by antigens like tuberculin, Candida, trichophyton and mumps.

The immune status of patients of tuberculosis was assessed by X-ray chest, blood count and skin test by antigen like E. Coli, M. catarhalis strepto aureus, A. influenzae, strep, viridans and Candida albicans and D.N.C.B. sensitization. Sensitization dose of 2,000 ug of D.N.C.B. in .1 ml of acetone was used; a control dose of 50 (j.g was also used in .1 ml acetone to see whether

patient is sensitised before or not. Challenge dose of 50 μ .g was used after 14 days, reaction was evaluated for three days in terms of erythema, induration, vesiculation and ulceration.

Table I shows the result of D.N.C.B. stimulation in hyporeactor and reactor to tuberculin. Patients of tuberculosis having reaction less than 10 mm are classified as hyporeactors. Reactors includes those with induration more than 10 mm. Out of 10 hyporeactors only 20% could be sensitized by D.N.C.B. whereas 80% of reactors could be sensitized. No significant difference was found in the lymphocyte count.

Table II shows results of intradermal test by bacterial and fungal antigen. 50 % of hyporeactors reacted to antigen of H. influenzae, N. catarhalis, Candida albicans. Reactions to antigen of E. Coli and strep, viridans were 40% and 10% respectively. Amongst the reactors to tuberculin 60%, 80% and 70% reacted to H. influenzae, N. catarhalis and E. Coli respectively. Reaction to strep, viridans and Candida was 30% and 70% respectively.

Table III shows correlation of D.N.C.B. sensitization and reaction to bacterial and fungal antigen in hyporeactors and reactors of tuberculin. 6 patients in hyporeactor group reacted to less than two bacterial and fungal antigens, 4 patients showed reaction to between 3 to 5 antigens, whereas 8 patients in reactor group showed reaction to 3 to 5 antigens, 16% of hyporeactors having reaction to less than 2 bacterial and fungal antigens could be sensitized by D.N.C.B., whereas amongst reactors to tuberculin, 75% patients reacting to 3 to 5 antigens could be sensitized by D.N.C.B.

D.N.C.B. is a simple chemical which produces active sensitization in 100% normal man indicating adequate cell mediated immunity. In the present study only 20% of hyporeactor tuberculous patients demonstrated sensitization to D.N.C.B. Thus 80% patients of this group had depressed cell mediated response.

Hyporeactor tuberculous patients reacted in only 40 % of intradermal tests done by antigens of common bacteria and fungi, whereas 62 % tests done by same antigen showed reaction in reactor tuberculous patients. This finding demonstrates that tuberculous patients who are hyporeactors

Table 1

Result of D.N.C.B. sensitization in hyporeactors and reactors in tuberculin

Tuberculin reaction	No. of cases	Stimulation by D.N.C.B.	Lymphocyte count
Hyporeactors	10	20%	Not significant
Reactors	10	80%	

Table II

Results of intradermal tests by bacterial and fungal antigens

Tuberculin reaction	H. Influenzae	N. Catarrh.	E. Coli	Strep. viridans	Candida albicans
Hyporeactors	50%	50%	40%	10%	50%
Reactors	60%	80%	70%	30%	70%

Table III

Correlation of D.N. C.B. sensitization and reaction of bacterial and fungal antigens

	No. of antigens	
	0—2...	3—5
Hyporeactors	6	4
D.N.C.B. sensitization	1 (16%)	1
Reactors	2	8
D.N.C.B. sensitization	2	6 (75%)

to tuberculin fail to react with other antigens more often than reactors to tuberculin.

60 % of hyporeactor tuberculous patients reacted to less than two bacterial and fungal antigens. Out of these only 16% could be sensitized to D.N.C.B. whereas amongst reactor tuberculous patients 75 % reacted to 3 to 5 antigens and 75 % of these patients could be sensitized by D.N.C.B. According to this observation tuber-

culous patients can be classified into two distinct groups.

- (a) Hyporeactive to tuberculin and other antigens, and can not be sensitized by D.N.C.B., indicating immune deficiency.
- (b) Reactive to tuberculin and other antigens and can be sensitized by D.N.C.B. indicating proper immune process.

According to this criteria 50% of Mantoux negative tuberculous patients have immune deficiency. This finding possibly explains individual to individual variation in response to same chemotherapy as host factor plays an important role in determining the ultimate outcome of chemotherapy.

In our undernourished population with immune deficiency, Mantoux negative test should not only mean non-infected, but this group includes those infected but still tuberculin negative due to depressed C.M.I. These Mantoux negative individuals are at a higher risk to develop disease because of low host resistance.

Immunity to Infection

Non-Specific Immunity (Innate)

- (1) Low pH of skin
- (2) Lysozyme-Bactericidal enzyme
- (3) Phagocytosis

Specific Immunity (Acquired)

- (1) Cell mediated reaction
- (2) Humoral antibody synthesis

Specific immunity operates in cooperation with non-specific immunity and increases its effectiveness.

Are Cellular and humoral systems essential for protection of man ?

- (1) Incidence of diseases in genetic humoral and cellular deficiencies.
- (2) Incidence of disease in acquired humoral and cellular deficiencies.
 - (i) Immune suppression
 - X-Rays
 - Cyto toxic drugs
 - Corticosteroids
 - (ii) Lymphoproliferative disorder
 - Lymphatic leukaemia
 - Myeloma

- (iii) Malnutrition
- (iv) Viral infections
 - Measles.

Clinical evidence of Immune deficiency

(A) Cell Mediated Immune deficiency

- (1) Recognisable just after birth
- (2) Common bacterial infection dealt with
- (3) Infection by Herpes Zoster virus and Thrush
- (4) Overwhelmed by vaccinia and measles and B.C.G.

(B) Humoral Immune Deficiency

- (1) Recognisable at age of 4 months
- (2) Presence of thrush (*Candida albicans*)
- (3) Prone to repeated infection by pyogenic bacteria
- (4) Measles and small pox—readily brought into control.

Immune deficiency predisposes to tuberculosis

- (1) Malnutrition
- (2) Corticosteroid
- (3) Measles
- (4) Hodgkins.

Patients with deficient C.M.I, are hypo or unreactive to skin test by antigen like tuberculin, *Candida*, *trichophyton* and mumps.

Negative Mantoux test in patients of tuberculosis may be an indication of deficient C.M.I. in those patient.

Assessment of Immune Status

- C.M.I. (1) X-ray chest
 (2) Blood count
 (3) Skin test by *E. Coli*, *Neisseria catarrhalis*, *staphylococcus aureus*, *haemophilus influenzae*, *Strep. viridans*, *Candida albicans*.
 (4) D.N.C.B. sensitization.