TUBERCULOUS MENINGITIS IN CHILDREN: MANIFESTATION OF AN IMMUNE COMPROMISED STATE

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ABSTRACT

Thirty children in the age group 0-4 years with tuberculous meningitis (TBM) were investigated for their immune status (cell-mediated and humoral). Twenty age, sex and nutritional status matched children were investigated on the same lines, who served as controls. Absolute T cell counts were significantly increased (3126 ± 1623) ($p < 0.01$) in TBM, though T cell percentages were comparable (59.8% in TBM versus 54.44% in controls). Leucocyte migration inhibition (LMI) test positivity was high (93%) in TBM patients. Mean LMI index showed a highly statistically significant difference ($p < 0.001$) between the 'Before-therapy' (0.62 ± 0.16) and 'During-therapy' (0.77 ± 0.23) groups in TBM patients. Mantoux test positivity with 1 TU of PPD was low (53.0%) in TBM in comparison to LMIT positivity. In humoral immune response, quantitative function measured by EAC rosettes was not altered. However, there was a significant decrease in the levels of IgA (79.48 ± 33.78 IU) ($p < 0.01$), IgG (115.01 ± 32.56 IU) ($p < 0.01$) and IgM (148.50 ± 51.88 IU) ($p < 0.05$) in TBM patients. There was no significant difference in the complement levels in the TBM and control groups. The results show a well developed CMI response but a poor humoral response in TBM and represent an inverse relationship between the CMI and humoral responses.

Key words: *Tuberculous meningitis, Cell-mediated immunity, Humoral immunity.*

The most common type of tuberculosis in children is pulmonary but the most dangerous form is that which affects the central nervous system. Tuberculous meningitis (TBM) is usually a complication of primary infection with or without miliary spread. Its incidence is directly proportional to the prevalence of tuberculous infection in a given community. Incidence of TBM in cases of tuberculosis varies from 7 to 12%(1,2). Out of a total of 16.46% deaths in pediatric wards due to tuberculosis of various types, TBM accounted for 56.1% in India(3).

Immunity in tuberculosis is widely accepted as being cell-mediated. The cooperation between macrophages and lymphocytes sensitized by antigens leads to the restriction of intracellular growth of the bacillus. Attention has also been given to the humoral immune response to tuberculous infections(4-6). There are few studies which have been done to look into the basic immune status of children with TBM(6-8). It is imperative to know the immune spectrum responsible for a varied clinical picture, with TBM having the severest. In the present study the 'cell-mediated immune response (CMIR) and humoral immune response in peripheral blood of children with TBM have been evaluated.

Material and Methods

Thirty children with TBM diagnosed

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with the criteria described elsewhere(9) in the age group of 0-4 years admitted to the Pediatric ward of All India Institute of Medical Sciences, New Delhi, were investigated for their immune status (cellular and humoral). For comparison 20 age, sex and nutritional status matched children serving as controls who had not received BCG vaccination and were Mantoux test negative, were also investigated. The nutritional status was assessed by weight for age criterion of Nutrition Subcommittee of Indian Academy of Pediatrics(10). The following immune parameters were investigated:

(A) Cell-mediated immune response

(*i*) The tuberculin intradermal Mantoux test as an *in-vivo* measure of CMIR with 1 TU of purified protein derivative (PPD, supplied by BCG Vaccine Laboratory, Madras). Induration of 10 mm or more after 48 hours was taken as a positive Mantoux test response.

(*ii*) T cell percentage and absolute counts in the peripheral blood of children of TBM and control groups by the sheep RBC rossette formation technique of Jondal *et al.*(11).

(*iii*) Leucocyte migration inhibition test (LMIT) using H37Ra strain of *Mycobacterium tuberculosis* as antigen by the technique of Soborg and Bendixen(12). A value of 0.8 or less of LMI in a child was considered as positive. The value of LMI index was obtained by the following calculations after recording the areas depicting the migration of leucocytes in the experiments conducted with the antigen and that without the antigen:

$$\text{LMI index} = \frac{\text{Area of migration with antigen}}{\text{Area of migration without antigen}} \times 100.$$

Fifteen of the 30 TBM children were investigated for LMIT and Mantoux test positivity, and LMI index before starting the antituberculous therapy and they constituted the 'Before-therapy' group while those investigated for these parameters during the course of antituberculous therapy formed the 'During-therapy' group and included 28 children. The 'During-therapy' group was investigated after 3 to 6 months of initiation of antituberculous therapy.

(B) Humoral immune response

(*i*) B cell percentage and absolute counts in the peripheral blood of children of TBM and control groups, by the method of Jondal *et al.*(11).

(*ii*) Serum immunoglobulins by the single radial immuno-diffusion technique of Mancini *et al.*(13). Serum complement (C_3) was estimated by the technique of Sirisinha *et al.*(14).

Results

Qut of a total of 30 children suffering from TBM only 4 (13.3%) had normal nutritional status whereas 19 (63.3%) had Grades I or II malnutrition and 7 (23.4%) had Grade III or IV malnutrition.

Quantitatively, there was an increase in absolute T cell counts ($p<0.01$) as a measure of cell-mediated immune response (*Table I*). Leucocyte migration inhibition test positivity was 93.3% in 'Before-therapy' group whereas it was 57.1% in 'During-therapy' group. Difference in these two groups is statistically significant ($p<0.05$). Mantoux test positivity did not show a significant difference between 'Before-therapy' (53.3%) and 'During-therapy' (53.5%) groups. Mean leucocyte migration inhibition index in the above two groups shows a statistically significant difference ($p<0.001$) (*Table II*).

TABLE I—*T and B Cell profile (Mean ± SD)*

Type of cases	T cell		B cell	
	%	Absolute No.	%	Absolute no.
TBM (n=30)	59.80±8.44	3126±1632	18.95±5.13	679±312
Control (n=20)	54.44±10.50	1840±1039	19.84±4.71	662±342
p value	NS	<0.01	NS	NS

NS = Not significant.

TABLE II—*Leucocyte Migration Inhibition Test (LMIT) and Mantoux Test Positivity, and LMI Index Profile*

Type of cases	Positivity No. (%)		LMI index (Mean ± SD)
	Mantoux	LMIT	
TBM Before-therapy (n=15)	8 (53.3)	14 (93.3)	0.62±0.16
During-therapy (n=28)	15 (53.5)	16 (57.1)	0.77±0.23
Control (n=20)	-	-	1.20±0.41
p value	NS	<0.05	>0.001*

NS = Not significant.
* Level of significance in comparison to 'Before-therapy' and 'During-therapy' groups.

There was no difference either in the percentage or absolute B cell counts in the diseased group as compared to the control group. However, the levels of all classes of the immunoglobulins were decreased in the TBM children which is statistically significant ($p<0.01$ for IgA and IgG; $p<0.05$ for IgM). There was no significant difference in the complement levels in these two study groups (*Table III*).

Discussion

One of the most potent host factors against tuberculous infection is the immune response. Therefore, evaluation of the immune status is considered pertinent to the understanding of the immunological profile of the disease.

TABLE III--*Serum Immunoglobulin (Ig) and Complement Profile (Mean ± SD)*

Type of cases	Immunoglobulin levels (IU)			Complement levels (mg/ml)
	IgA	IgG	IgM	
TBM (n=30)	79.48±33.78	115.01±32.56	148.50±51.88	0.651±0.27
Control (n=20)	109.63±43.22	149.75±52.13	208.35±107.81	0.537±0.27
p value	<0.01	<0.01	<0.05	NS

NS = Not significant.

The cell-mediated immune response against tubercle bacilli in children with TBM in the present study was quite well developed as measured by LMIT. LMIT positivity was high (93.3%) in the 'Before-therapy' group in comparison to the 'During-therapy' group (57.1%) ($p<0.05$). The low LMIT positivity in the 'During-therapy' group as compared to the 'Before-therapy' group is reflected by the fact that even partial or inadequate antituberculous therapy results in improved T lymphocyte functions(15). However, Mantoux test positivity was quite low in comparison to LMIT positivity. It is well established that Mantoux test positivity is affected by associated malnutrition while LMIT is better elicited in malnutrition as it has direct relationship with the degree of malnutrition(16). Percentage of T cells in the peripheral blood was also found to be comparable in TBM patients and controls which is in conformity with the earlier studies(7,8) because cell-mediated immunity in tuberculosis relates more to the functional aspect of T lymphocytes (qualitatively sensitized to tuberculous antigen) than to the quantitative aspect(7). Nagar and Higasshi(17), however, have observed fewer active (E_1) and total (E_2) T lymphocytes in the peripheral blood. In the present study B cell percentage and absolute B cell counts are comparable in diseased group and controls; similar results were also observed by other workers(6-8).

There are conflicting reports regarding immunoglobulin profile in TBM patients. In a recent study by Murthy *et al.*(5), the immunoglobulins in serum and cerebrospinal fluid of TBM patients were raised while in other studies the serum immunoglobulins were reported to be decreased(6-8). Decreased immunoglobulin levels in our study are in conformity with these reports and with the fact that recurrent infections in children result in decreased serum immunoglobulin levels(18). Since control children were age- and nutritional status-matched, the low serum immunoglobulin levels in TBM group can be attributed to the tuberculous meningitis disease and not to the accompanying malnutrition factor.

Further, a number of chronic diseases such as leprosy(19), sarcoidosis and rheumatoid arthritis exhibit an inverse relationship between cell-mediated and humoral immunity and it is inferred that tuberculosis may also be an example of this type of an inverse relationship, though the cause for

this is not known. Later, Lenzini *et al.*(20) have described an immune spectrum in pulmonary tuberculosis in adults, dividing the patients into polar reactive and unreactive groups and an intermediate reactive/ unreactive group showing characteristics of the two polar groups. The immunological findings in the present study suggest that TBM in children can be classified as a reactive intermediate type as evident by the positive LMIT response and the depressed humoral response with low antibody levels of all classes of immunoglobulins. These immunological classifications when translated to the clinical patterns of the disease have important therapeutic significance; the reactive form with positive cell-mediated response exhibiting a marked early response to antituberculous therapy while the unreactive form with absent or very poor cell-mediated response showing a poor response to therapy(20).

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NOTES AND NEWS

VINOD K. KAPUR RESEARCH SCHOLARSHIP

Applications are invited for the Dr. Kapur's Pediatric Surgery Research Scholarship and Travelling Fellowship for the year 1994 amounting to Rs. 25,000 and Rs. 10,000, respectively. Handwritten applications for the same should be submitted to the office of Bai Jerbai Wadia Hospital for Children and Research Centre, Department of Pediatric Surgery, Acharya Donde Marg, Parel, Bombay 400 012 by the end of *October 1993.* The results will be notified to the successful candidates by post after scrutiny of the applications by the Chairman, Dr. V.K. Kapur and other members of the selection committee. The applicants have to be of Indian origin and graduates of recognized Indian Medical University. The project can be of clinical importance or basic science contributing towards progress of child health care.