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Bacterial meningitis: T cell activation and immunoregulatory CD4⁺ T cell subset alteration

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Meningitis is the most important cause of acquired postnatal deafness and neurologic disorders in children. To determine if cell-mediated immunity is casually related to the pathogenesis of bacterial meningitis, T cell subsets were quantitated from blood of the 29 children with clinical and bacteriologic diagnosis of Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitidis bacterial meningitis. The CD4⁺ T cells increased and CD8⁺ T cells decreased in patients with meningitis as compared to patient control subjects (bacterial infections without meningitis) and normal healthy control subjects. An elevated percentage of CD25⁺ (interleukin-2 receptors) and HLA-DR⁺ (immune-response gene-associated antigen) T cells were detected from all patients with meningitis. All 29 patients with meningitis had highly elevated CD4⁺ CD45R⁺ (suppressor-inducer) cells and reciprocally depressed CD4⁺ CDw29⁺ (helper-inducer) cells compared with healthy age-matched normal and patient control subjects. These findings indicate characteristic immunologic T cell abnormalities from meningitis. The abnormal increase in the CD4⁺ CD45R⁺ suppressor-inducer or "virgin" cells and expression of activation antigens on T cells may be of help in future understanding of abnormal immune reactions from bacterial meningitis. However, deficiency of the CD4⁺ CDw29⁺ helper-inducer or "memory" cells may contribute to the impaired helper function for B cell-induced protective antibody synthesis to bacterial capsular polysaccharides found in this disease. (J ALLERGY CLIN IMMUNOL 1991;87:1115-20.)

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The human CD3⁺ T-lymphocytes possess two reciprocally exclusive compartments of CD4⁺ helper/inducer and CD8⁺ suppressor/cytotoxic T cell subsets.¹ CD4⁺ T cells are the major cells that carry the memory, initiation, and regulation of the immune response. Functionally distinct subpopulations of CD4⁺ T cells have been defined recently with MAb recognizing cell-surface markers. The CD4⁺ T cells expressing CD45R Ag is a "virgin" cell displaying a suppressor-inducer function, whereas those CD4⁺ T cells lacking CD45R but expressing CDw29 Ag exhibit a helper-inducer function and is a "memory" cell.²⁻⁵ In the face of an antigenic challenge by viral, fungal, protozoan, or bacterial pathogen, these CD4⁺ T cells are activated to fulfill their individual functional programs. Severe alterations in these CD4⁺ T cell subsets have been associated with several human diseases.⁶⁻¹¹

Bacterial meningitis remains a major cause of morbidity and mortality in children in much of the world. *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* infections are the most common causes of meningitis in Saudi Arabia and elsewhere.^{12, 13} Infectious diseases are associated so intimately with the function of the immune system that it would be possible to classify specific and severe infection on the basis of cellular and humoral immune mechanisms. Therefore, to correlate with the specific T cell abnormality, if this is present, we have determined the percentage distribution of T cell subsets from circulation of patients with *H. influenzae*, *S. pneumoniae*, and *N. meningitidis* bacterial meningitis. Our results presented here demonstrate that these patients with bacterial meningitis have an increased percentage of CD25⁺- and HLA-DR⁺-activated T cells, and the most marked abnormality was an increase of the CD4⁺ CD45R⁺ (suppressor-inducer, virgin) and a decrease of CD4⁺ CDw29⁺ (helper-inducer, memory) cells.

METHODS

Patients

Patients (total 29) with definite bacterial meningitis established by clinical signs and heavy positive bacterial cultures from both CSF and blood, who were admitted either to the pediatric ward, Asir Central Hospital, Abha, or Lassan Hospital, Abha, were eligible for this study. Fifteen children (mean age, 2.3 years; nine male and six female children) had *H. influenzae* meningitis. CSF and blood cultures were positive for *H. influenzae* type B microorganisms from all 15 children.¹⁴ CSF and blood cultures of eight children (mean age, 2.6 years; six male and two female children) grew *S. pneumoniae*, and cultures of six children (mean age, 2.1 years; five female and one male child) grew *N. meningitidis*. All patients with meningitis had fever, irritability, and lethargy, and most patients had additional

Abbreviations used

MNC:	Mononuclear cell
MAB:	Monoclonal antibody
CSF:	Cerebrospinal fluid
NK:	Natural killer
IL-2R:	Interleukin-2 receptor
Ab:	Antibody
Ag:	Antigen

signs, such as neck stiffness, bulging anterior fontanelle, and convulsions. Eight patients without meningitis but proven bacterial infection (three with *Klebsiella pneumoniae*, two with *S. pneumoniae*, two with *Staphylococcus aureus*, and one with *H. influenzae*) served as patient control subjects. Blood samples were withdrawn from patients and patient control subjects after diagnosis of disease and before commencement of therapy. Fifteen healthy children served as normal control subjects. Patient control subjects (infection without meningitis) and normal control subjects were age- and sex-matched as closely as possible.

T cell studies

Peripheral blood MNCs isolated by Histopaque-1077 (Sigma Chemical Co., St. Louis, Mo.) density-gradient centrifugation were analyzed with the following MABs: OKT3 (CD3⁺ total T cells), OKT4 (CD4⁺ helper/inducer T cells), OKT8 (CD8⁺ suppressor/cytotoxic T cells), OKB2 (CD24⁺ pan-B cells), OKMI (CD11⁺ monocytes), Leu-7 (CD57⁺ NK cells), anti-IL-2R (CD25⁺ IL-2R), and OKIa1 (HLA-DR⁺ cells) (Ortho Diagnostics, Raritan, N.J., and Becton Dickinson, Mountain View, Calif.) by the indirect immunofluorescence technique described recently.^{10, 11}

MNCs were depleted of macrophages by adherence to plastic. The macrophage-depleted MNCs were rosetted with neuraminidase-treated sheep erythrocytes.¹¹ T cells (erythrocyte rosetting) were separated by Histopaque-1077 gradient centrifugation, and erythrocytes were removed by lysing with 0.83% ammonium chloride Tris-buffer solution. This method yielded 92% to 95% CD3⁺ T cells. The CD4⁺ (92% to 96% OKT4 MAb reactive) and CD8⁺ (91% to 94% OKT8 MAb reactive) subsets were purified from the CD3⁺ total T cells by a panning technique with OKT8 and OKT4 MAb solutions, respectively, as previously described.¹¹ The percentage distribution of activation Ags, CD25⁺ and HLA-DR⁺, was determined from the total CD3⁺, CD4⁺, and CD8⁺ T cells; 2H4 (anti-CD45R) and 4B4 (anti-CDw29) MAb staining was done to determine suppressor-inducer (CD4⁺ CD45R⁺) and helper-inducer (CD4⁺ CDw29⁺) T cell subsets from the purified CD4⁺ T cells by the method as previously described.^{10, 11}

RESULTS

As presented in Table I, the CD4⁺ T cells increased and CD8⁺ T cells decreased from circulation of all patients with bacterial meningitis compared to patient control subjects (bacterial infection without menin-

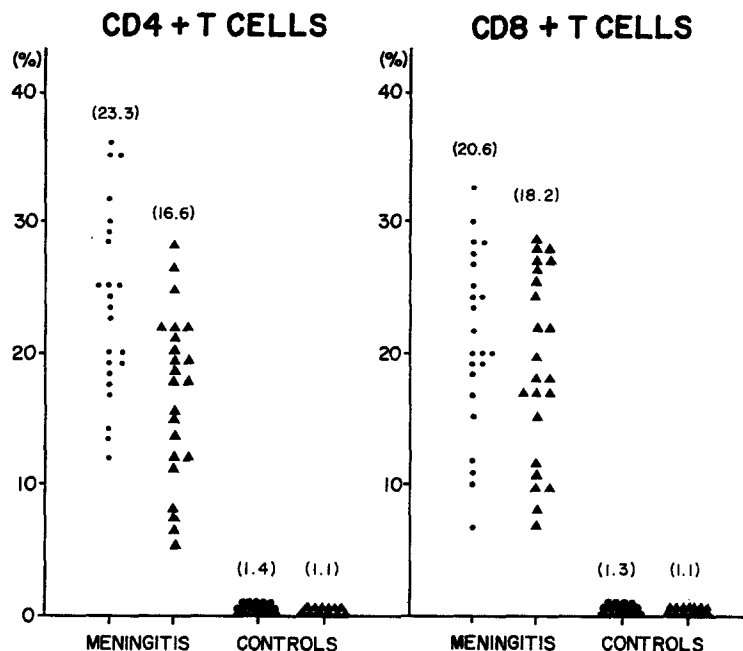


FIG. 1. CD25⁺ (●) and HLA-DR⁺ (▲) cells in purified CD4⁺ and CD8⁺ T cell subsets from *H. influenzae* and *S. pneumoniae* meningitis (N = 23) and normal control subjects (N = 15). Mean data are presented in parentheses.

TABLE I. MAb-defined phenotypic characterization of MNCs

	Percentage of positive staining with specific MAbs								
	CD24 ⁺ B cells	CD11 ⁺ monocytes	CD57 ⁺ NK cells	CD3 ⁺ T cells	CD4 ⁺ helper T cells	CD8 ⁺ suppressor T cells	CD25	IL-2R	Ia ⁺ HLA-DR
Subjects with bacterial meningitis* N = 29	8.6 ± 2.1	5.2 ± 1.2	10.8 ± 1.7†	73.8 ± 4.5	58.4 ± 5.0†	16.4 ± 3.6†	24.7 ± 3.0†	25.5 ± 3.4†	
Patient control subjects‡ N = 8	13.8 ± 2.3	9.7 ± 1.5	6.2 ± 1.3	70.5 ± 5.2	42.5 ± 4.6	27.2 ± 4.1	3.8 ± 1.2	10.4 ± 1.6	
Normal control subjects N = 15	11.4 ± 2.6	8.8 ± 2.0	5.7 ± 1.6	67.2 ± 4.5	41.3 ± 5.1	25.2 ± 3.4	1.7 ± 0.4	7.4 ± 1.2	

*Patients with *H. influenzae*, *S. pneumoniae*, and *N. meningitidis* bacterial meningitis.

†*p* < 0.001 as compared to patient control subjects and normal control subjects (determined by Student's *t* test).

‡Patients with *H. influenzae*, *S. pneumoniae*, *S. aureus*, and *K. pneumoniae* infection but without meningitis.

gitis) and normal healthy control subjects (*p* < 0.001). The patients with meningitis also demonstrated an increased percentage of CD57⁺ NK cells, CD25⁺ cells (IL-2R), and HLA-DR⁺ cells. However, total B cells (CD24⁺) and monocytes (CD11⁺) were lower in patients with meningitis than in the control subjects.

Patients with meningitis had a highly increased percentage of CD25⁺ and HLA-DR⁺ cells in MNCs.

HLA-DR⁺ Ags are present on normal B cells and some monocytes.¹⁵ However, both CD25⁺ and HLA-DR⁺ Ags are also markers of activated T cells and are present in very low concentrations on normal resting T cells. A striking increase of CD25⁺ and HLA-DR⁺ cells was evident from the purified CD3⁺ total T cells of all patients with meningitis (7% to 33%) compared to patient control subjects (0% to 8%) and normal healthy control subjects (0% to 3%). We de-

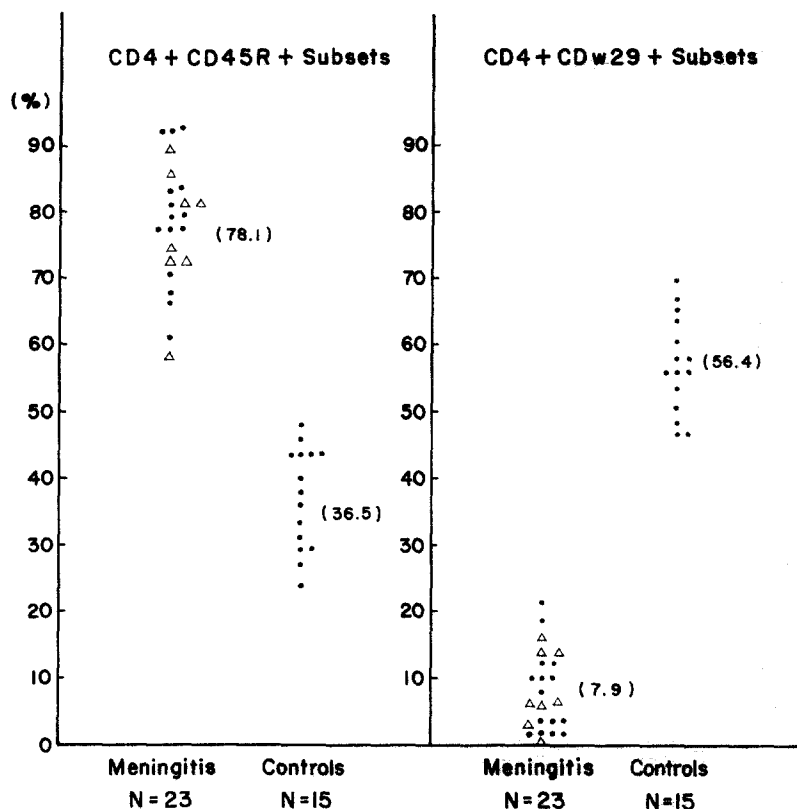


FIG. 2. The percentage distribution of CD4⁺ CD45R⁺ (suppressor-inducer) and CD4⁺ CDw29⁺ (helper-inducer) T cell subsets in blood. Dots identify *H. influenzae*, and triangles identify *S. pneumoniae*, meningitis. Mean data are presented in parentheses.

terminated the expression of CD25⁺ and HLA-DR⁺ Ags from the purified CD4⁺ and CD8⁺ T cell subsets of 23 patients with *H. influenzae* and *S. pneumoniae* meningitis. These data, illustrated in Fig. 1, demonstrated that both of these activation Ags, CD25⁺ and HLA-DR⁺, were expressed almost equally in both CD4⁺ and CD8⁺ T cell populations. Patients with *N. meningitidis* bacterial meningitis also had elevated levels of the CD25⁺ and HLA-DR⁺ Ags in the purified CD3⁺ T cells but were not investigated for distribution of these Ags in the CD4⁺ and CD8⁺ T cell subsets. It was assumed that, similar to other bacterial meningitis (illustrated in Fig. 1), these patients with *N. meningitidis* may also have almost equal distribution of CD25⁺ and HLA-DR⁺ activation Ags in the CD4⁺ and CD8⁺ T cell subsets.

These data, illustrated in Fig. 2, demonstrated an alteration in the immunoregulatory CD4⁺ T cell subsets from patients with *H. influenzae* and *S. pneumoniae* bacterial meningitis, with the most marked abnormality being an increase of the CD4⁺ CD45R⁺ (suppressor-inducer) and a decrease of the CD4⁺ CDw29⁺ (helper-inducer) subsets. Similarly, all pa-

tients with *N. meningitidis* bacterial meningitis also demonstrated an elevation in the CD4⁺ CD45R⁺ (81.4% ± 6%) and deficiency in the CD4⁺ CDw29⁺ (14.6% ± 3%) T cell subsets from circulation. However, it is important to note that this study determined that patient control subjects who had bacterial infections (*K. pneumoniae*, *S. pneumoniae*, *S. aureus*, or *H. influenzae*) but without meningitis had almost similar levels of the CD4⁺ CD45R⁺ (46.3% ± 5%) and CD4⁺ CDw29⁺ (48.6% ± 5%) T cell subsets, as was demonstrated for normal control subjects (Fig. 2).

DISCUSSION

Bacterial meningitis in children remains an important cause of death and major neurologic damage among survivors.^{12,13} In essence, any severe infectious disease with high morbidity and mortality rate implies that the immune defence system has been successfully breached. However, to our knowledge, immunodeficiencies related to abnormality or deficiency of T cell subsets have never been described as a result of meningitis. Our results demonstrated that patients with bacterial meningitis have characteristically in-

creased percentage of CD25⁺ (IL-2R) and HLA-DR⁺ (immune-response gene-associated Ag) Ags in the CD3⁺ T cells. Of interest, an important immunoregulatory CD4⁺ T cell subset abnormality, with increased representations of the suppressor-inducer (CD4⁺ CD45R⁺) and reciprocal depressions of the helper-inducer (CD4⁺ CDw29⁺) cells in blood, characterizes *H. influenzae*, *S. pneumoniae*, and *N. meningitidis* meningitis. Thus, a primary event in this disease may trigger the cell-mediated immunity and the immunoregulatory network responds by modifying the delicate balance of suppressor-inducer and helper-inducer T cell subsets. It is also important to document here that the simple bacterial infection without meningitis does not result in such specific CD4⁺ T cell subset abnormalities in circulation.

The study on characterization of immunoregulatory CD4⁺ T cell subsets, which should play a leading role in immune response and disease pathogenesis, has just now begun.⁶⁻¹¹ The inability of infants and young children to produce protective Ab to bacterial capsular polysaccharides is responsible for increased incidence of bacterial meningitis. In view of the role of T cells as helper cells for B cell Ab production, and the regulatory functions of CD4⁺ CD45R⁺ and CD4⁺ CDw29⁺ subsets in immune homeostasis, enumeration of these CD4⁺ T cell subsets is relevant to an understanding of immune reactions operative in meningitis. Recent evidence indicates that CD4⁺ CDw29⁺ T cells exhibit helper-inducer function for pokeweed mitogen-driven IgG synthesis and Ag-specific Ab production.^{2,8} Therefore, based on our results reported here, it is assumed that a deficiency of the CD4⁺ CDw29⁺ helper-inducer T cell subsets may be important in deficient production of protective Ab to bacterial capsular polysaccharides in this disease. It is also possible that these alterations in the CD4⁺ CD45R⁺ and CD4⁺ CDw29⁺ subsets may predispose these patients to other complications. In addition, CD4⁺ CD45R⁺ subsets may represent virgin or naive cells, and CD4⁺ CDw29⁺ subsets may represent memory cells,⁴ and thus, the abnormality observed may represent a block in differentiation. Clearly, additional studies are important to substantiate our findings.

Circulating CD25⁺ and HLA-DR⁺ T cells have been demonstrated previously from some human diseases of bacterial and viral etiology as well as in autoimmunity.¹⁶⁻²⁰ T cell activation may lead to secretion of certain lymphokines, such as interleukins, interferons, tumor necrosis factors, or lymphotoxins (neuroleukins), which may cause adverse effects on cellular structures in the body.²⁰⁻²² T cell activation and abnormal increase of the CD4⁺ CD45R⁺ subsets may

release certain specific cytokines/lymphokines that may induce some kinds of neurologic deficits and other inflammatory processes characteristic of meningitis. Earlier, from two other situations, in tuberculosis pleuritis and in granulomatous disease, leprosy, concentrated CD4⁺ CDw29⁺ T cell subsets were detected at the site of tissue inflammation, which provided insights into the immunopathogenesis of these disorders in humans.^{9, 23} Similarly, multiple sclerosis is defined as a T cell-mediated neurologic disorder caused by the presence of CD25⁺ and HLA-DR⁺ T cells and immunoregulatory abnormalities in CD4⁺ T cell subsets.^{6, 24, 25} Meningitis is a very important disease of children. Additional characterization of the functional attributes of activated T cells and CD4⁺ CD45R⁺ and CD4⁺ CDw29⁺ subsets will aid in the additional understanding of immune mechanisms of the disease pathogenesis.

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An in vitro model of peptide-mediated immunomodulation of the human T cell response to *Dermatophagoides* spp (house dust mite)

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Allergic sensitivity of Dermatophagoides spp (house dust mites) is mediated by specific IgE antibody, the production of which requires the presence of CD4⁺ helper T cells. Attempts to hyposensitize this response in allergic individuals have depended on the administration of extracts of specific allergen. However, the ability of peptides derived from unrelated antigens to inhibit specific immune responses offers an alternative approach to therapy. We have addressed this question by examining the ability of a nonstimulatory peptide analogue derived from influenza virus hemagglutinin to modulate T cell recognition of house dust mite. The peptide inhibited the response of mite-specific CD4⁺ T cell clones restricted by either the HLA-DRB1 or DRB3 gene products. Furthermore, mite-induced polyclonal T cell responses were negatively modulated by the peptide, whereas recognition of common recall antigens remained intact. The inhibitory effects were mediated at the level of the antigen-presenting cell, since no inhibition of mitogen or anti-CD3 antibody-driven T cell proliferation was observed. In direct binding assays, the peptide analogue bound to selected HLA-DR molecules expressed on the membrane of antigen-presenting cells, with specificity predominantly for those class II proteins capable of restricting house dust mite-allergen T cell recognition. (J ALLERGY CLIN IMMUNOL 1991;87:1120-7.)

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