Objective: To investigate some aspects of T-cell–dependent immune function in patients with dementia of the Alzheimer type (DAT).

Design: Assay of interleukin 6 binding on T lymphocytes from patients with DAT, compared with that in healthy controls.

Setting: The study included ambulatory patients in a tertiary care center who were diagnosed as having DAT according to the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke.

Subjects: Thirty-five patients with DAT without depression (15 women and 20 men; mean ± SD age, 68.6 ± 15.8 years) were selected consecutively. They had not taken any medication for at least 3 weeks and did not smoke. Illness severity was evaluated according to the Clinical Dementia Rating Scale. Thirty-five age- and sex-matched healthy nonsmoking subjects with no family history of neuropsychiatric disorders formed the control group.

Results: A significant (P < .001) increase in T-lymphocyte interleukin 6 binding was found in patients with DAT compared with healthy controls (mean ± SE receptors per cell, 305 ± 7 vs 276 ± 6, respectively), whereas the ligand-receptor affinity values were similar in the 2 groups (mean ± SE, 25.9 ± 0.9 and 25.3 ± 0.6 nmol/L).

Conclusion: These data indicate a derangement of the immune response in patients with DAT since cell-surface interleukin 6 receptors seem to be related to T-lymphocyte immune function.

Arch Neurol. 1998;55:1305-1308

Activation of the immune system function may be an integral component of the pathological changes occurring in Alzheimer disease (AD). CD4+ and CD8+ cells have been detected in large numbers in the hippocampus and temporal cortex in patients with AD.1-3 Interleukin 2 receptor (IL-2R) and HLA-DR are profusely expressed in the brain cortices of patients with AD: HLA-DR immunoreactivity colocalizes with all neuritic plaques.2-4 The levels of immunoreactive IL-1β, IL-2, and IL-3 are increased, and IL-1β labeled with iodine I 125 and [125I]IL-2 binding are markedly elevated in the hippocampus in patients with AD.3 Reactive microglial cells express major histocompatibility complex molecules, lymphocyte function–associated antigen 1, receptors for the Fc chain, C3, C4, and vitronectin.1-4 Since microglial cells express both HLA-DR and lymphocyte function–associated antigen 1 (the adhesion molecule for intercellular adhesion molecule 1), they may serve to mediate antigen presentation functions. The complement proteins C1q, C4d, C3d, and C5b-9 have been found in dystrophic neuritis, neuropile threads, and some neurofibrillary tangles.3,6 Proteins designed to defend against bystander lysis caused by the membrane attack complex, C8 binding protein, and vitronectin, have been associated with damaged neuronal processes in patients with AD.6 Such data suggest that the autodestructive process, the glial proliferation, and the scavenger activity characteristic of AD may occur in an immune context.

Based on the suggested role of the immune system in the pathogenesis and pathophysiological mechanism of AD and the discoveries about neuroimmune networks, studies of the systemic immune function in patients with AD have sometimes yielded discordant results.7 In one study, the peripheral blood lymphocytes (PBLs) from patients with AD showed higher proliferative response to IL-2 and glial fibrillary acidic protein, a typical glial cell marker, than PBLs from age-matched healthy controls.8

From the Department of Neurosciences, University of Pisa, Pisa, Italy.
The CD4+ cell–mediated helper activity is lower in patients with AD and senile dementia of the Alzheimer type (DAT) than in healthy elderly individuals. CD8+ cell-mediated suppressor function is lower in patients with AD and senile dementia of the Alzheimer type (DAT) than in healthy elderly individuals. The natural killer cell activity in patients with DAT is significantly lower than in healthy elderly individuals. A high incidence of autoantibodies to brain myelin basic protein and thymic cells, enhanced immunocyte expression of the brain-derived S100 protein, increased serum levels of soluble CD8 antigen, and enhanced IL-1, IL-2, and IL-6 production have been reported in patients with AD.

In the search for novel neuroimmune markers specifically related to the cell-mediated immunity that seems to be altered in AD, we assayed T-lymphocyte binding for interferon gamma (a T cell–type cytokine) in patients with DAT. We found significantly (P < .001) reduced binding for interferon gamma in patients compared with age-matched controls.
patients with DAT and in age-matched healthy controls. In elderly controls, interleukin 6 immunoreactivity has been shown in plaques of AD brains and correlated with the transformation of diffuse into neuritic plaques and the development of dementia. Interleukin 6 has a wide variety of biological functions, including induction of T-cell growth and differentiation and induction of nerve cell differentiation. Interleukin 6 immunoreactivity has been shown in plaques of AD brains and correlated with the transformation of diffuse into neuritic plaques and the development of dementia. Serum or cerebrospinal fluid levels of IL-6 are not significantly different in patients with AD compared with control subjects, however, elevated IL-6 concentrations were measured in the brains of patients with AD. The production of IL-6 by peripheral blood mononuclear cells is significantly higher in patients with AD than in patients with vascular dementia and elderly controls, suggesting a possible role for IL-6 in the pathogenesis of AD.

Interleukin 6 mediates its biological effects through binding to a single class of specific cell-surface high-affinity receptors, expressed mainly on T lymphocytes, mitogen-stimulated B cells, granulocytes, and monocytes. After IL-6 binds to its receptor, this complex interacts with a signal-transducing receptor component, gp130, inducing disulfide-linked homodimerization and tyrosine phosphorylation of gp130, finally causing the activation of Janus kinases 1 and 2.

We found that human T cells from patients with DAT and healthy controls express high-affinity IL-6 receptors. The binding of [125I]IL-6 was specific because only unlabeled IL-6 significantly inhibited the binding (by nearly 88%), whereas the same amounts (100 ng) of IL-1, IL-3, IL-4, tumor necrosis factor alpha, interferon alfa, interferon beta, and interferon gamma were ineffective. Scatchard analysis of the data yielded a linear plot, representing a single-binding site model. Saturation binding experiments revealed similar results.

We found no significant differences in dissociation constant values between patients with DAT and healthy controls (mean ± SE, 25.9 ± 0.9 vs 25.3 ± 0.6 nmol/L), but highly significant differences in maximal receptor number values between the 2 subject groups (Figure 1) (mean ± SE receptors per cell, 305 ± 7 vs 276 ± 6).

In a subset of patients and controls (n = 15), we reassayed T-cell IL-6 receptor binding after 2 and 4 weeks and found similar results, namely, significantly higher maximal receptor number values in patients than in controls, and similar dissociation constant values in the 2 subject groups (Figure 2).

No significant differences in T-lymphocyte IL-6 receptor density were observed between men and women in the patient and control groups (Table), and subject age did not affect maximal receptor number values. No correlation was found between maximal receptor number values and illness severity (data not shown).

The central nervous system has traditionally been regarded as an immunoprivileged site; however, the demonstration of immune cells in DAT senile plaques and neurofibrillary tangles supports the hypothesis that immune response plays a role in the pathogenesis and pathophysiological mechanism of DAT. Recent studies have
shown that the blood-brain barrier is not as impervious as previously believed: there is evidence for an active and highly regulated communication between the central nervous system and the peripheral immune system.33

Local derangement of the blood-brain barrier in patients with DAT may facilitate bidirectional passage of cytokines between the central nervous system and systemic circulation.34 In patients with DAT, biochemical abnormalities in PBLs related to disease activity have been found37: in the course of immune aging, activated auto-

abnormalities in PBLs related to disease activity have been found37: in the course of immune aging, activated auto-

receptors per cell, 532 ± 21 vs 275 ± 17). Such results parallel those of other researchers,39,40 who assayed an enhanced number of high-affinity IL-6 receptors on activated T cells compared with resting T lymphocytes while studying the modulation of IL-6 receptor expression during in vitro T-cell activation.

Our results of a significantly increased number of T-cell IL-6 receptors in patients with DAT compared with healthy controls may indicate in vivo T-cell activation in DAT.

We think that the search for novel specific neuro-immune markers, such as certain cytokine receptors on PBLs, is important for the development of diagnostic and therapeutic strategies for AD.

Accepted for publication April 20, 1998.

Reprints: Paolo Bongioanni, MD, PhD, Department of Neurosciences, University of Pisa, 56126 Pisa, Italy (e-mail: bongioanni@sssup1.sssup.it).

REFERENCES

1. Itagaki S, McGeer PL, Akiyama H. Presence of T-lymphotactic suppressor and leu-

kocyte common antigen positive cells in Alzheimer’s disease brain tissue. Neu-


2. Rogers J, Leber-Narod J, Styren SD, Cavin WH. Expression of immune system-


5. Araujo DM, Lapchak PA. Induction of immune system mediators in the hippocam-


8. Nakamura K, Takeda M, Tanaka T, et al. Glial fibrillary acidic protein stimulates proliferation and immunoglobulin synthesis of lymphocytes from Alzheimer’s dis-


11. Araga S, Kajimoto H, Runamoto K, Takahashi K. Reduced natural killer cell ac-


84:259-263.

12. Singh VK. Studies of immunomarker responses in Alzheimer’s disease. Mol Neu-


1253-1256.


macroglobulin immunoreactivity in cortex and hippocampus of Alzheimer’s dis-


19. Hull M, Berger M, Volk B. Bauer J. Occurrence of interleukin-6 in cortical plaques of Alzheimer’s disease patients may precede transformation of diffuse into neu-


tex: no changes in mature IL-1β or IL-1α but increases in the associated acute phase proteins IL-6, α2-macroglobulin and C-reactive protein. Brain Res. 1993;

629:245-252.

22. Huberman M, Sredni B, Stem L, et al. IL-2 and IL-6 secretion in dementia: cor-


25. Taga T, Hibii M, Hirata Y, et al. Interleukin-6 triggers the association of its recep-


27. Stahl M, Boulton TG, Farrugella T, et al. Association and activation of Jak-Tyk ki-


23:56-62.


33. Kalaria RN. The immunopathology of Alzheimer’s disease and some related dis-


34. McRae A, Dahlstrom A. Immune responses in brains of Alzheimer’s and Parkin-


35. Czerr HA, Knopf PM. Cervical lymphatics, the blood brain barrier and the immu-


38. Huberman M, Shalit F, Roth-Deri I, et al. Correlation of cytokine secretion by mono-


89:192-198.


conjugated interleukin-6 to in vitro-activated human peripheral blood mono-
