

Physiologic Modulation of Natural Killer Cell Activity As An Early Marker Of Alzheimer's Disease

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In our previous work, we established that patients with mild cognitive impairment and short history of senile dementia of the Alzheimer's type (sDAT) show abnormal responsiveness of natural killer (NK) cell activity in response to certain physiological modifiers, such as cortisol. We also reported that the spontaneous activity of this innate immune cell population remains within normal range. Patients with Alzheimer's disease (AD) might be characterized by altered sensitivity to cortisol-mediated modulation of circulating lymphocytes. We proposed that longitudinal studies are needed to address the clinical applicability of these abnormalities as prognostic factors. Following this line of work, we designed a longitudinal study to address the clinical applicability of physiologic modulation of NK cell activity as a prognostic factor in AD. We followed 18 subjects (age range: 61-84 years old) with mild sDAT under treatment with acetylcholinesterase inhibitors (Donepezil 10 mg/daily), and 10 healthy control subjects (59-79 years of age). The change in time for several rating scales [Mini Mental State Examination (MMSE), Functional Assessment Staging (FAST), Center for Epidemiological Studies-Depression (CES-D) and Profiles of Mood States (POMS)] was analyzed in parallel to immunophenotypic parameters of T cells, and the response of NK activity to physiological modulation. Psychoimmune measures were obtained at entry and at six months intervals for 18 months. NK activity was assessed as baseline measurement and in response to modulation by cortisol at 10^{-6} M. To verify the immunophysiological integrity of the NK cell population, we tested augmentation of NK cytotoxicity by human recombinant interleukin (IL)-2 (100 IU/ml) as control. Neither the percent or number of NK cells, nor baseline NK cell cytotoxic activity were different in sDAT patients compared to their matched control cohorts at entry. By contrast, the response to modulation by cortisol or by IL-2 was significantly greater in patients with sDAT. The change in circulating CD3+Dr+ population with time in patients with sDAT was significantly inversely correlated with the change in time in the response of NK cytotoxic activity to cortisol modulation in these patients, suggesting an underlying immunological mechanism. Based on change in the MMSE score at entry and at 18 months, patients with sDAT were assigned to a "fast progression" ($\square > 2$ points) or to a "slow progression" group ($\square < 2$ points). The change in the response of NK cytotoxic activity to cortisol, and the strength of the association of this parameter with circulating activated T cells in time was greater in patients with Fast Progression, compared to Slow Progression sDAT. Taken together, our findings reveal an increased sensitivity to cortisol in patients with sDAT, which can be detected systemically at the level of the cellular compartment of the immune system. The results suggest that changes in the response of NK cells to negative (e.g., cortisol) or positive modifiers (e.g., IL-2) follow progression of sDAT, and might be an adequate early psychoimmune marker of AD. We propose that the measurement of NK activity may be an inexpensive and accessible tool for the assessment of risk, and for the early diagnosis and follow-up of sDAT. Acknowledgments: This work was supported in part by Fondazione Cassa di Risparmio di Cuneo; Fondazione Cassa di Risparmio di Saluzzo; NIDDKD P50 DK 64539; and the Alzheimer's Association.