

strategies for neurodegenerative diseases, as recently suggested by the Syst-Eur trial.

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Rate of cognitive decline in AD is accelerated by the interleukin-1 α –889 *1 allele

Article abstract—The reason for differences in rate of cognitive decline in AD is unknown. The interleukin-1 α (IL-1 α) –889 *2 allele is associated with increased risk for AD. Surprisingly, in a sample of 114 patients followed for an average of 3.8 years, individuals homozygous for the IL-1 α –889 *1 allele declined significantly more rapidly on the Mini-Mental State Examination than did others. There was no difference in rate of decline between patients with and without the *APOE* ϵ 4 allele. These results support the hypothesis that inflammation is important in the clinical course of AD.

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It is not known why some patients with AD decline rapidly, whereas others decline more gradually. No genetic factor has been consistently linked to rate of cognitive decline. The *APOE* ϵ 4 allele, the major genetic risk factor for AD, has no effect on rate of decline in patients with AD.^{1–3} Understanding factors

that affect rate of decline in AD is important to patients, families, and clinicians.

Inflammation may contribute to AD pathophysiology.⁴ Potentially neurotoxic mediators of inflammation such as interleukin-1 (IL-1) are expressed at abnormally high levels by glial cells in AD and may lead to neuronal injury. Recently, polymorphisms at the IL-1 α , IL-1 β , and the IL-1 receptor antagonist (IL-1ra) loci have been shown to increase the risk for AD.^{5–7} Although the effects of these genetic variants on the expression and function of IL-1 α , IL-1 β , and IL-1ra in the brain are unknown, it is possible that they augment inflammation, thus contributing to neurodegeneration. We tested the hypothesis that the IL-1 α promoter –889 *1/*2 polymorphism affects the rate at which patients decline once they develop AD. For comparison, the effect of the *APOE* ϵ 4 allele on rate of decline was also examined.

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Table Mean slopes of MMSE scores regressed on age for the three IL-1 α -889 genotype groups and for APOE ϵ 4 carriers and noncarriers

Genotype	N	Mean slope MMSE points per year	SD
IL-1α -889			
*1/*1 Genotype	48	-4.5	2.8
*1/*2 Genotype	52	-3.4	1.7
*2/*2 Genotype	14	-3.0	2.1
Total	114	-3.8	2.4
APOE			
ϵ 4 Noncarrier	48	-3.9	1.8
ϵ 4 Carrier	66	-3.8	2.7
Total	114	-3.8	2.4

MMSE = Mini-Mental State Examination.

Methods. Patients with probable AD (59 men, 55 women) were included in the study. Diagnosis was made by National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria as previously described.² The mean age at onset of AD was 67.4 years (SD = 8.4), with a range of 47 to 87 years. A total of 103 subjects were white, two were African American, three were Hispanic, and seven were Asian. Cognition was assessed with the Mini-Mental State Examination (MMSE). The mean number of MMSE evaluations per patient was 6.4 (SD = 2.7) over a mean interval of 3.8 years (SD = 1.9). To determine rate of cognitive decline, we estimated slopes by using a linear regression of MMSE scores on age as previously described.² Slopes were expressed as MMSE points per year. Only MMSE scores between 23 and the first instance of a zero score were included in the analysis to avoid ceiling and floor effects.

Genomic DNA extraction from frozen ethylenediaminetetraacetic acid-containing whole blood or buccal mucosa samples and APOE genotyping were performed as previously described.² Genotyping for the IL-1 α -889 *1/*2 polymorphism was performed, blind to clinical data, according to the method of McDowell et al.⁸

To compare MMSE slopes among genotype groups (table), a general linear model analysis of variance was used with gender as a second fixed factor and age at which the first MMSE score was obtained as a covariate. Least significant difference tests were used for post-hoc testing. To compare other continuous variables among genotype groups, one-way analyses of variance were used. To compare categorical variables among genotype groups χ^2 analyses were used.

Results. The mean change in MMSE score per year was different among the three IL-1 α -889 genotype groups (F = 3.72, *df* = 2,107, *p* = 0.027). Least significant difference tests showed that *1 homozygotes had a greater mean rate of decline than heterozygotes and *2 homozygotes (*p* = 0.02). Mean rates of decline for heterozygotes and *2 homozygotes were not significantly different. Additional analyses of variance showed that there were no differences

between IL-1 α -889 *1 homozygotes and other patients in age at onset of AD, time between disease onset and first MMSE score, number of MMSE scores collected, number of years over which MMSE scores were obtained, or in years of education. χ^2 analyses showed that the three IL-1 α -889 genotype groups did not significantly differ in number of males and females, number of patients placed in nursing homes during the study period, or in number of subjects who had taken tacrine or donepezil during the study period. When the 20 subjects who had taken tacrine or donepezil at some point during the study were excluded from the analysis, the effect of IL-1 α genotype was still evident (F = 3.76, *df* = 2,87, *p* = 0.027). The IL-1 α genotype groups did not differ in the number of whites and nonwhites, and after exclusion of the 12 nonwhites from the analysis the effect of IL-1 α genotype was still present (F = 3.29, *df* = 2,96, *p* = 0.04). There was no difference in rate of cognitive decline between patients with and without the APOE ϵ 4 allele in a general linear model analysis of variance (F = 0.012, *df* = 1,109, NS).

Allele frequencies for the IL-1 α -889 polymorphism were 0.65 for the *1 allele and 0.35 for the *2 allele. These values are virtually identical to those reported for other samples of patients with AD.^{6,7} APOE allele frequencies were ϵ 2 = 0.04, ϵ 3 = 0.59, and ϵ 4 = 0.37, values typical for AD samples.

Discussion. These results indicate that the IL-1 α -889 polymorphism affects rate of decline in AD, with individuals homozygous for the *1 allele declining more rapidly than other subjects. Prior results suggest that the *2 allele increases the risk for AD. It is unclear why the *2 allele increases the risk for disease onset, but results in a slower rate of decline once the disease becomes manifest. Little is known about the time course of expression of IL-1 in AD or about its time-specific interactions with the myriad of other proinflammatory factors present in the plaque lesion. As noted by Rogers,⁴ the biology behind the initiation of the inflammatory response in AD may differ from that which sustains it. Thus, the role of IL-1 in AD pathology may change during the course of the disease. Further, recent A β immunization experiments⁹ suggest that some aspects of the inflammatory reaction in AD, such as microgliosis, which is stimulated by IL-1,¹⁰ may retard AD pathology through clearance of A β . Finally, it is possible that in prior cross-sectional association studies⁵⁻⁷ *1 carriers were under-represented owing to more rapid decline. In any case, it may be simplistic to assume that genetic risk factors for AD will always increase the rate of cognitive decline. This is clearly demonstrated by results from this and other studies showing that for the APOE ϵ 4 allele disease risk and rate of decline are not correlated.

Many factors such as concurrent medical illness, quality of daily care, and stability of living situation can affect the rate at which patients with AD decline cognitively. These factors were not addressed in the current study or in most other studies on genetic determinants of rate of cognitive decline. Further, other means of quantifying cognitive decline may yield differ-

ing results. Thus, our results demonstrating an effect of the IL-1 α -889 promoter polymorphism on rate of decline in AD must be replicated in other independent samples. Nevertheless, this polymorphism should be considered as a potential pharmacogenetic marker for response to anti-inflammatory agents designed to slow rate of cognitive decline in AD.

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Hypothalamic amnesia with spontaneous confabulations: A clinicopathologic study

Article abstract—Previous studies demonstrated that patients producing spontaneous confabulations fail to suppress currently irrelevant memory traces and have anterior limbic lesions, particularly involving the orbitofrontal cortex or the basal forebrain. Here, a woman is described who had sarcoidosis damaging the medial hypothalamus and endocrine dysfunction, and a severe memory failure characterized by spontaneous confabulation, disorientation, and severely impaired free recall with preserved recognition. Isolated hypothalamic damage may produce the same type of memory disorder as orbitofrontal damage.

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Patients producing spontaneous confabulations are convinced about the veracity of their thoughts and occasionally act according to their confabulations.¹⁻³ We found that spontaneous confabulators specifically fail to distinguish between memories that pertain to ongoing reality and memories that do not,² a failure based on an inability to suppress currently irrelevant memories.^{3,4} Lesions always involve anterior limbic structures, in particular, the orbitofrontal cortex or its connections in the basal forebrain.^{3,5,6}

Hypothalamic lesions may produce an amnesia, rarely with confabulations,⁷ which has been attributed to damage of the mammillary bodies.⁷⁻⁹ Here, we report an anatomoclinical study of a woman with a discrete hypothalamic lesion causing endocrine dysfunction and severe amnesia with spontaneous confabulations and disorientation.

Case report. A 67-year-old right-handed woman with 12 years of education was admitted because of a 2-year history of hyperphagia, hyperdipsia, and forgetfulness. She had started to consume high quantities of foods and drank \approx 6 L of water a day. She occasionally fell asleep during daily activities. Her affect seemed "sluggish" and indifferent. Despite general apathy, she had occasional bursts of rage with screaming.

She would repeatedly ask for the current date, month, or even year but soon forget the answer. Memory for remote events appeared intact. She often produced confabulations and occasionally acted on them. For example, although she had retired as a committee member of a local party and from her responsibilities in the local church 4

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