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ORIGINAL PAPER

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# Polymorphisms of the gene encoding the inflammatory cytokine interleukin-6 determine the magnitude of the increase in soluble interleukin-6 receptor levels in Alzheimer's disease

## Results of a pilot study

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**Abstract** Interleukin-6 (IL-6) is a multifunctional cytokine involved in the pathogenesis of Alzheimer's disease (AD). The effects of IL-6 are mediated through a specific receptor complex made up of a ligand binding glycoprotein (gp80 or IL-6R) and a signal transducing glycoprotein (gp130). Conflicting results have been reported concerning altered IL-6 or soluble IL-6R (sIL-6R) levels in serum and CSF in AD. This study investigated whether genetic heterogeneity determines the magnitude of the difference in IL-6 and sIL-6R levels in AD. Fifty-eight AD patients and 25 control subjects were included. Plasma and CSF IL-6 and sIL-6R levels were measured and the IL-6 variable number of number repeats (*IL-6vntr*) and IL-6 promoter (*IL-6prom*) genotypes were determined. sIL-6R levels in plasma and CSF were higher in AD patients than in control subjects. This elevation was striking among non-carriers of the *IL-6vntr*C* allele and among subjects homozygous for the *IL-6prom*C* allele whereas no difference in plasma and CSF sIL-6R levels was observed among carriers of the *IL-6vntr*C* allele and among subjects with the *IL-6prom*CG* and *IL-6prom*GG* genotypes. We conclude that plasma and CSF levels of sIL-6R are significantly increased in AD patients and that the magnitude of increase is determined by the IL-6 genotype.

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## Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder and the most frequent cause of dementia in the elderly. The main neuropathological features of AD are accumulation of β-amyloid peptide (βA4), generation of neurofibrillary tangles, and loss of neurons.

AD-associated neurodegeneration might function as immune stimulus resulting in the production of inflammatory cytokines. Interleukin-6 (IL-6) is a multifunctional cytokine produced by a variety of cells involved in inflammatory response. It mediates various, partially opposite functions in the nervous system such as neuronal cell growth and differentiation or neuronal degeneration. There is growing evidence suggesting that the inflammatory response and in particular IL-6 play an important role in the pathogenesis of AD: I) elevated IL-6 immunoreactivity was observed close to amyloid plaques in brains of AD patients [Strauss et al. 1992], II) IL-6 provokes induction of the synthesis of β-amyloid precursor protein [Vandenabeele and Fiers, 1991], III) epidemiological studies showed that anti-inflammatory medication was associated with delayed onset of AD [Breitner, 1996], IV) in transgenic mouse models elevated CNS levels of IL-6 result in neuropathogenic effects and cognitive deficits [Campbell et al. 1997], V) genetic variations of IL-6 influenced the risk and onset age of AD [Papassotiropoulos et al. 1999, Bagli et al. 2000, Shibata et al. 2002].

The functional effects of IL-6 are mediated through a specific receptor complex made up of a ligand binding glycoprotein (gp80 or IL-6R) and a signal transducing glycoprotein (gp130) [Kishimoto et al. 1992]. IL-6 first binds to IL-6R. The IL-6/IL-6R complex subsequently binds to the gp130 signal-transducing receptor subunit.

Soluble forms of IL-6R (sIL-6R) and gp130 (sgp130) play a physiologic role in IL-6 signalling. sIL-6R is able to bind to IL-6 and the IL-6/sIL-6R complex activates the gp130 transducer chain. In contrast to this agonistic feature of sIL-6R, a negative regulatory mechanism has been proposed for sgp130. The biological effect of IL-6 is counteracted by binding to sgp130 [Narazaki et al. 1993].

The role of cytokines in the pathogenesis of AD and their significance in clinical monitoring of the disease progression has received increasing attention. However, conflicting results have been reported concerning altered IL-6 levels in serum or CSF in AD; some authors described increased levels [Blum-Degen et al. 1995, Kalman et al. 1997, Licastro et al. 2000, Maes et al. 1999], one report found decreased IL-6 levels in AD [Yamada et al. 1995], while others did not find significant differences [Angelis et al. 1998, Garlind et al. 1999, Hampel et al. 1997, Lanzrein et al. 1998, Marz et al. 1997, van Duijn et al. 1990]. The same contradictory data exist for sIL-6R. A decrease in sIL-6R concentration in AD has been reported by two groups [Angelis et al. 1998, Hampel et al. 1998], whereas Marz and colleagues found no alterations in the sIL-6 levels in AD patients [Marz et al. 1997].

A significant overlap of IL-6 and sIL-6R-concentrations in plasma or CSF may be observed between AD patients and controls, which may partially explain the contradictory results in the literature. However, this overlap may be due to genetic heterogeneity among subjects. We recently reported that the C allele of a variable number tandem repeat (VNTR) polymorphism of the IL-6 gene (*IL-6vntr*C*) was associated with a delayed initial onset and reduced AD risk [Papassotiropoulos et al. 1999]. Additionally, the haplotype consisting of the IL-6vntr*C allele and the C allele of a G/C promoter polymorphism at position –174 of the IL6 gene (*IL-6prom*C*) also influences the AD risk [Bagli et al. 2000]. Consequently, the aim of the present study was to compare the plasma and CSF levels of IL-6 and sIL-6R in AD and non-AD patients and to assess their relationship to the IL-6 genotypes.

## Subjects and methods

### Subjects (Table 1)

Thirty-one AD patients and 25 subjects comprising a mixed control group were recruited from the Department of Psychiatry of the University of Bonn. An additional group of 27 AD patients were enrolled from the Department of Psychiatry, Ludwig-Maximilian-University Munich. The group of the 25 non-AD patients consisted of 6 depressed patients, 6 subjects with mild cognitive impairment, 12 patients with vascular dementia, and 1 patient with alcohol-related dementia. Patients with acute or chronic inflammatory disorders and patients receiving anti-inflammatory medication were excluded. All participants underwent clinical examination including medical and family history, general medical and neurological examination, psychiatric interview, laboratory tests, neuropsychological testing, and CT or MRI brain scans. The diagnosis of AD was performed according to the NINCDS-ADRDA criteria (McKhann et al. 1984). The cognitive status was measured by the Mini Mental State Examination (MMSE) and Structured Interview for the Diagnosis of Alzheimer Dementia and Dementias of other Aetiology (SIDAM). The study was approved by the Ethics Committees of the participating institutions. All participants gave informed consent.

**Table 1** Demographic data, clinical characteristics, and APOE ε4 allele distribution

| | AD patients | Non-AD patients |
|---|---|---|
| Total number | 58 | 25 |
| Gender (males/females) | 22/36 | 11/14 |
| Age (years)* Mean ± SD | 71.2±8.6 | 65.4±10.5 |
| MMSE** Mean ± SD | 19.4±5.0 | 24.5±4.4 |
| APOE ε4 allele*** (present/absent) | 40/18 | 9/16 |

* $t = 2.6$, $df = 81$, $P = 0.01$
** $t = 4.1$, $df = 73$, $P < 0.001$
*** Fisher's exact test: $P = 0.005$
*MMSE* Mini Mental State Examination; *APOE* apolipoprotein E genotype

### Determination of IL-6 and sIL-6R

Blood samples were drawn by venous puncture and collected into EDTA tubes. After centrifugation for 15 min at 4000 g and at 4 °C the plasma was separated and stored at –80 °C. CSF was taken by lumbar puncture, immediately shipped on ice, and stored at –80°C for subsequent analysis. Plasma and CSF IL-6 and sIL-6R levels were determined in duplicate using commercially available ELISA kits Quantikine® (R&D Systems, Wiesbaden-Nordenstadt, Germany). The minimum detectable concentration of IL-6 and sIL-6R was 0.15 pg/ml and 16 pg/ml, respectively. The intra-assay coefficient of variation was below 5 %.

### Assessment of APOE and IL-6vntr genotypes

Genomic DNA was isolated from blood with the Qiagen® blood isolation kit according to the instructions provided by the manufacturer (Qiagen, Hilden, Germany).

The IL-6vntr was studied by a single-step polymerase chain reaction (PCR) method.[22] Following oligonucleotide primers were used: 5'-GCA ACT TTG AGT GTG TCA CG-3' (forward) and 5'-TGA CGT GAT GGA TGC AAC AC-3' (reverse). The PCR amplification products were separated by 7 % polyacrylamide gel electrophoresis and visualized by silver staining. The PCR product sizes of the IL-6vntr variants in our study approximated the fragment size of four IL-6vntr allele classes published by Bowcock et al. (1989). The expected allele classes were IL-6vntr*A, *B, *C, and *D.

The determination of the IL-6prom polymorphism was based on a restriction-fragment length polymorphism (RFLP) analysis. The PCR was performed using the forward primer 5'-CAG AAG AAC TCA GAT GAC TGG-3' and the reverse primer 5'-GCT GGG CTC CTG GAG GGG-3'. The PCR product was digested with Sfa NI and the fragments were separated on an agarose gel. After ethidium bromide staining the two alleles were identified by their RFLP pattern: 367 bp and 244 bp for the C allele (*IL-6prom*C*) and 611 bp for the G allele (*IL-6prom*G*).

The APOE genotype was determined by the polymerase chain reaction restriction-fragment length polymorphism (PCR-RFLP) method [Hixson and Vernier, 1990].

### Statistical analysis

The Pearson's correlation coefficient was used for analyses of correlation between metric variables. After assessment of normal distribution by the Kolmogorov-Smirnov test, comparison of means between groups was performed by the Student's t-test. Allele frequencies were

compared using the Fisher's exact test. Where statistical testing was hypothesis-driven one-tailed significance was calculated, otherwise, two-tailed significance was estimated. The level of significance was set at $p \leq 0.05$. All statistical analyses were performed with SPSS for Windows, Version 9.0.1 (SPSS Inc., Chicago, Ill., USA).

## Results

sIL-6R and IL-6 plasma and CSF levels did not differ significantly between subjects of the mixed control group as determined by means of ANOVA ($p > 0.2$). Therefore, these subjects were pooled for further statistical analysis.

### IL-6 and sIL-6R levels in the different diagnostic groups (Table 2)

sIL-6R levels in plasma and CSF were higher in AD patients than in control subjects. While the difference in plasma was significant ($t = 2.0$, $df = 80$, $p = 0.024$), only a trend was observed in the CSF ($t = 1.2$, $df = 79$, $p = 0.112$). These differences were also confirmed using a randomly selected, age-matched sample of 46 AD patients and the 25 control subjects. sIL-6R plasma levels were higher in AD patients than in controls ($p = 0.022$). Again, only a trend was observed in the CSF ($p = 0.09$).

No difference in plasma and CSF concentrations of IL-6 between AD patients and controls was observed ($p > 0.5$). Multifactorial ANOVA revealed a significant effect of the interaction between the diagnosis and the IL-6 genotype (independent variables) on sIL-6R levels in plasma and CSF (dependent variables). The additional independent variables (APOE genotype, gender, and educational level) and the interactions between these variables with diagnosis did not influence significantly sIL-6R levels in plasma and CSF.

### sIL-6R levels in relation to the IL-6 genotypes (Fig. 1)

To assess the impact of the genetic background on the difference of IL-6 parameters between AD patients and control subjects, the study population was stratified ac-

**Table 2** Plasma and CSF levels of IL-6 and sIL-6R in AD patients and control subjects

| | AD patients | Control subjects | AD patients | Control subjects |
|---|---|---|---|---|
| | Plasma | | CSF | |
| IL-6 (ng/l) | 2.55±2.24 | 2.55±3.37 | 2.42±1.12 | 2.71±2.64 |
| SIL-6R (µg/l) | 34.8±9.1[a] | 30.6±8.1[a] | 0.98±0.27[b] | 0.91±0.22[b] |

[a] $t = 2.0$, $df = 80$, $p = 0.024$; [b] $t = 1.2$, $df = 79$, $p = 0.112$

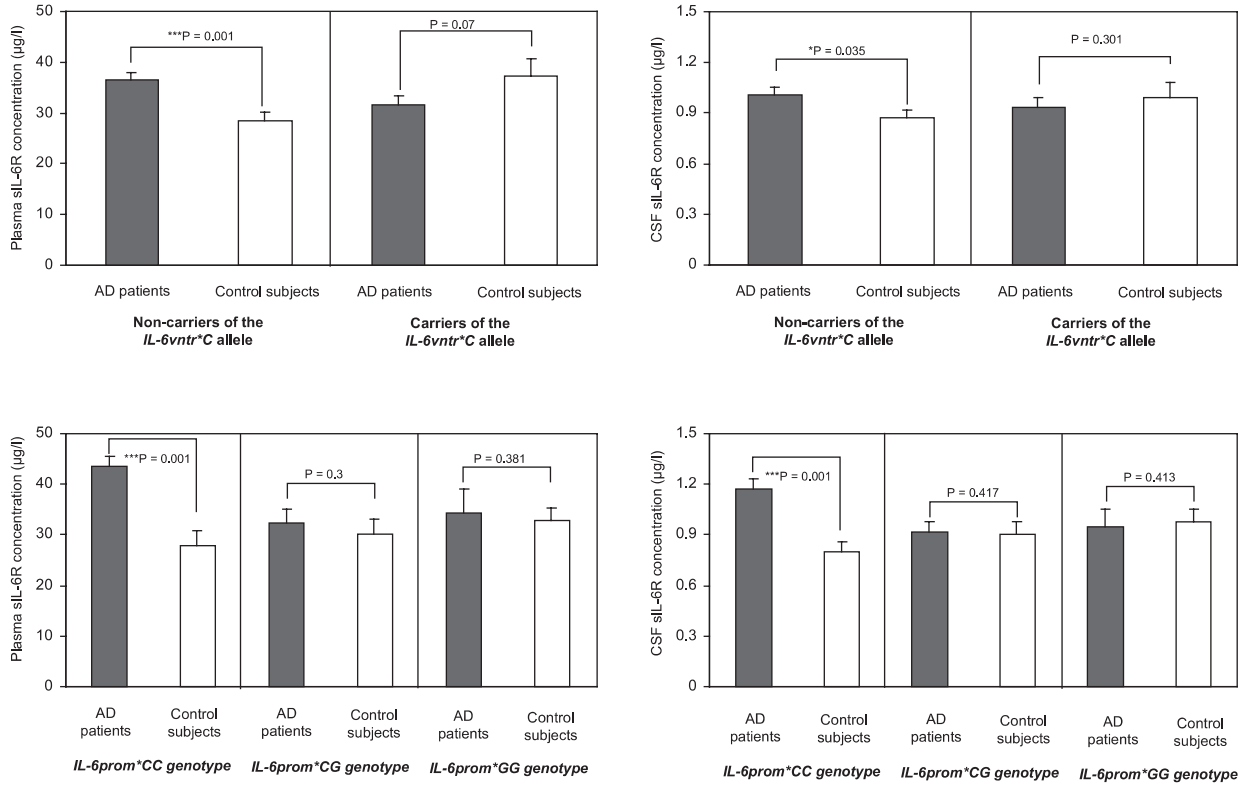


**Fig. 1** Plasma and CSF levels of sIL-6R in AD patients and control subjects in relation to IL-6 genotypes

cording to *IL-6vntr* and *IL-6prom* genotypes. In the case of the *IL-6vntr* polymorphism, study participants were divided in carriers and non-carriers of the C allele, since this allele was shown to influence the risk for AD in previous studies. Significant differences in plasma and CSF sIL-6R levels between AD patients and control subjects were observed in non-carriers of the *IL-6vntr*C* allele ($t = 3.2$, $df = 54$, $p = 0.001$ and $t = 1.9$, $df = 52$, $p = 0.035$, respectively). In carriers of the *IL-6vntr*C* allele, no difference was observed in plasma and CSF sIL-6R levels between AD patients and controls ($t = 1.5$, $df = 24$, $p = 0.07$ and $t = 0.5$, $df = 25$, $p = 0.301$, respectively). Stratification of study participants according to the *IL-6prom* genotype demonstrated the influence of this genetic factor on sIL-6R levels: in the group of participants homozygous for the *IL-6prom*C* allele, AD patients had markedly increased sIL-6R plasma levels compared to the non-AD group ($t = 4.5$, $df = 10$, $p = 0.001$). This also applied for the differences in sIL-6R CSF levels between AD patients and control subjects ($t = 4.8$, $df = 10$, $p = 0.001$). In the groups of *IL-6prom*CG* heterozygotes or *IL6-prom*GG* homozygotes, no differences in plasma or CSF sIL-6R levels between AD patients and control subjects were observed ($p \geq 0.3$ for all comparisons).

### Correlation analyses

Correlation analysis revealed a significant positive relationship between plasma and CSF sIL-6R levels in AD patients and control subjects ($r = 0.426$, $n = 55$, $p < 0.001$ and $r = 0.620$, $n = 25$, $p < 0.001$, respectively), but there was no such correlation between plasma and CSF IL-6. A positive correlation was detected between IL-6 plasma levels and age in AD patients and controls ($r = 0.302$, $n = 58$, $p = 0.021$ and $r = 0.453$, $n = 24$, $p < 0.026$, respectively). No significant correlations in patients and control subjects were detected between IL-6 CSF levels and age, sIL-6R plasma levels and age, and sIL-6R CSF levels and age. In AD patients, no significant correlations between cognitive performance as represented by the MMSE score and IL-6 plasma, IL-6 CSF, sIL-6R plasma, and sIL-6R CSF levels were observed.

## Discussion

In the present study we show that plasma and CSF levels of sIL-6R are significantly increased in AD patients and that the magnitude of increase is determined by the IL-6 genotype. This increase is independent of dementia severity. We do not observe detectable changes in plasma and CSF IL-6 levels between AD patients and control subjects. The age-associated increase in IL-6 levels in plasma is in accordance with previous observations [Ershler and Keller, 2000].

Under physiological conditions the effects of inflammation are directed against harmful pathogenic stimuli. However, an inappropriate or prolonged immune activation may lead to tissue damage. A dysregulated immune response has been proposed for patients with AD. Microglia activation together with activation of IL-6-mediated neuroimmune response have been proposed as part of a vicious circle potentiating neuronal degeneration. This dysregulation may be reflected by altered levels of cytokines and their receptors. Recent observations suggest that cytokine expression contributes differentially to the vulnerability of independent cortical regions during the clinical progression of AD [Luterman et al. 2000]. However, contradictory reports exist in the literature with respect to altered levels of IL-6 and sIL-6R in CSF or plasma in AD. Such discrepant results may be due to methodological factors, e. g. differences of the sensitivity of the commercial kits, sample preparation, selection of the biological specimens (CSF or plasma), and selection of patients and appropriate controls (healthy controls, or patients with disorders other than AD), but also due to additional factors like genetic and sociodemographic heterogeneity.

We show that the genetic variability of IL-6 significantly determines the magnitude of difference of plasma and CSF sIL-6R levels between AD and non-AD patients. Interestingly, a very recent study in a European Italian population confirms the genetic association between IL-6 and AD and underpins the importance of genetic heterogeneity when assessing differences of IL-6 parameters between AD patients and control subjects [Licastro et al. manuscript submitted].

Our results are in accordance with reports demonstrating that AD patients' IL-6 concentration in CSF or plasma do not correlate with disease severity and that IL-6 concentrations in AD patients are similar compared to non-AD patients or healthy controls. The observed correlation between plasma and CSF sIL-6R levels may indicate similar regulation of peripheral and central sIL-6R. Whether increased peripheral levels of sIL-6R represent neuroimmune alteration of the CNS remains unclear.

In conclusion, we show that plasma and CSF levels of sIL-6R in patients with AD are higher than in non-AD patients. Moreover, polymorphisms of the IL-6 gene, and in particular the C alleles of the IL-6 VNTR and promoter polymorphisms, which have been shown to reduce IL-6 activity and concentration in vivo, determine the differences in plasma and CSF sIL-6R levels. Consequently, our observations suggest a genetically determined regulation of the IL-6 and sIL-6R-mediated neuroimmune response in AD.

The study is limited by the fact that a sufficiently large collection of CSF samples of age-matched healthy control subjects could not be received even though time-consuming efforts had been made. Since few of these specimens of healthy age-matched could be included, the present investigation must be seen as a pilot study needing further replication.

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