Eur Arch Psychiatry Clin Neurosci (2003) 253 : 100 – 102 DOI 10.1007/s00406-003-0415-8

ORIGINAL PAPER

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Cerebrospinal fluid tau protein levels in schizophrenia

Received: 20 August 2002 / Accepted: 18 March 2003

Abstract Increased cerebrospinal fluid (CSF) tau protein levels are generally considered to provide a sensitive marker of neurodegenerative processes such as Alzheimer's disease (AD). Since a more pronounced cognitive decline has been described in older schizophrenic patients, it has been hypothesized that these patients might be at a higher risk of developing AD. CSF levels of total tau protein and tau protein phosphorylated at threonine 181 (phospho-tau) were determined among 19 older and younger patients with schizophrenia compared to 20 age-matched healthy controls. No significant differences in CSF total tau and phospho-tau levels arose between patients with schizophrenia and controls. Although our results do not exclude a progressive neurodegenerative pathology, they provide evidence against major neuronal degeneration such as an AD-related pathology associated with increased tau levels in schizophrenia.

Key words schizophrenia · tau protein · CSF · Alzheimer's disease · dementia

Introduction

In a recent six-year follow-up study of cognitive and functional status across the lifespan, different age-related patterns of cognitive change in institutionalized schizophrenic patients compared with Alzheimer's disease (AD) patients and controls were delineated (Friedmann et al. 2001). Patients with schizophrenia but not controls showed a significant decrease in Mini Mental State Examination (MMSE; Folstein et al. 1975) interval scores with age, with the older schizophrenic patients showing greater decline in MMSE scores during follow-up than the younger ones. Since the above-mentioned study deliberately selected younger schizophrenic patients with very poor prognosis for their similarity to the geriatric patients, it was concluded that progressive cognitive decline is not apparent in younger patients but may occur in those over age 65. This observation led to the hypothesis of a higher risk of cognitive decline in older patients which may be associated with neurodegenerative dementia in particular AD (Häfner et al. 2001).

However, until the potential impact of neurodegenerative processes on old age schizophrenia without manifest dementia is not clarified further the etiology of cognitive decline in those patients cannot be analyzed sufficiently. In the present study, we therefore investigated the cerebrospinal fluid (CSF) concentration of total and phosphorylated tau protein in samples of younger and older schizophrenic patients compared to age-matched controls. CSF total tau levels are generally considered a sensitive marker of the neurodegenerative processes characteristic for AD (Schönknecht et al. in press[a]). The fraction of CSF tau protein phosphorylated at threonine 181 was found to be even more specific for dementia with neurofibrillary pathology such as AD than total tau CSF levels (Blennow et al. 2001). This finding also applied for patients with mild cognitive impairment or early AD (Buerger et al. 2002). Although organic factors are still considered in the etiology of old age schizophrenia (Roth and Kay 1998), CSF tau protein levels have not been investigated in schizophrenia so far.

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Methods

Included were 10 young (age range: 21–38 years) and 9 patients of older age (age range: 54–70 years) with schizophrenia (DSM-IV). Manifest dementia could be excluded in all patients as well as persistent negative symptoms. Patients were consecutively admitted inpatients of the Department of Psychiatry, University Hospital Heidelberg. Clinical diagnosis was based on all relevant information including history, clinical examination, neuropsychological, and neuroradiological findings. All patients received neuroleptic treatment. In all patients, lumbar puncture was performed at a fixed time of the day (between 10 and 12 am) as part of the routine diagnostic procedure to exclude inflammatory disease. The control group consisted of 20 individuals without cognitive impairment or psychiatric disease, matched for age and gender, from whom CSF samples were obtained during spinal anesthesia at the Department of Anesthesia, University Hospital Heidelberg. The resultant CSF samples were immediately aliquoted into non-adsorbent tubes and frozen at –80 °C. Tau was measured using the Innotest htau antigen kit (Innogenetics, Zwijndrecht, Belgium), an ELISA constructed to measure the total amount of tau, i. e., both unphosphorylated and phosphorylated fraction (Blennow et al. 1995). The Innotest-Phospho-Tau(181P) ELISA was used to measure tau protein phosphorylated at threonine 181 (phospho-tau) (Vanmechelen et al. 2000). For data analysis, Pearson correlation coefficients, analyses of variance (Duncan's test) and/or covariance, and χ^2 tests were calculated.

Results

Patients and controls were of comparable age and showed a similar gender distribution (Table 1). Compared to the older controls (MMSE score: 29.5 (± 0.6), range: 28 to 30), older schizophrenic patients had significantly lower but still above dementia level MMSE scores (27.7 (± 1.9), range: 25 to 30). Among the older schizophrenic patients, only two had MMSE scores less than 27 due to a slightly reduced attentional and visuo-spatial performance.

When young and elderly schizophrenic patients were compared with controls, only minor, non-significant differences in CSF total tau and phospho-tau levels arose. However, when compared across groups there was a non-significant trend towards higher total tau and phospho-tau levels in the elderly. Total and phospho-tau levels were significantly correlated in both young ($r = 0.9$, $p < 0.05$) and elderly ($r = 0.9$, $p < 0.05$) schizophrenics, and in young ($r = 0.9$, $p < 0.05$) and elderly ($r = 0.8$, $p < 0.05$) controls. Neither in the young nor in the group of elderly patients with schizophrenia were total and phospho-tau levels significantly correlated with age, age at onset or MMSE scores. With respect to total and phospho-tau levels, there were no significant gender differences neither in the schizophrenic group nor in the controls.

Discussion

This is the first study to investigate CSF tau protein levels in schizophrenia. According to the present findings, patients with schizophrenia do not show increased CSF tau levels. Elevated tau protein levels which are characteristic for a neurodegenerative pathology such as AD were found neither in the schizophrenic group as a whole nor in the subgroup of elderly schizophrenic patients. Since increased CSF total tau and phospho-tau levels are generally considered to be sensitive markers of neurodegeneration in AD, we could not conclude from the results of this study that older schizophrenic patients might have an increased risk of developing AD. Consequently, the previous finding of greater cognitive decline in the older schizophrenic patients compared with the younger patients (Friedman et al. 2001) seems to be attributable rather to schizophrenia itself than to a concomitant neurodegenerative pathology such as AD. This hypothesis is also supported by our recent finding that total tau and phospho-tau levels were already significantly elevated in a group of patients with incipient AD who presented with MMSE scores in a range similar to that of the elderly schizophrenic patients investigated here (Schönknecht et al. 2003).

Although a significant age effect was not found, the elderly subjects in our study tended to have the highest tau and phospho-tau levels irrespective of diagnosis. This finding is consistent with a recent study of a large number of 231 healthy subjects indicating an age-dependency of CSF tau protein levels (Sjögren et al. 1999).

The finding of normal CSF total tau and phospho-tau protein levels may have important clinical implications for the early diagnosis of AD in patients with schizophrenia in that an increase of the CSF tau concentration

Table 1 Clinical characteristics and CSF total and phospho-tau levels in patients and controls with the results of a Duncan's test at the 5 % level

	Schizophrenia age > 50 years n = 9 g1	Schizophrenia age < 50 years n = 10 g2	Controls age > 50 years n = 10 g3	Controls age < 50 years n = 10 g4	Duncan's test ($p < 0.05$)
Sex (f/m)	6/3	3/7	6/4	5/5	not applied
Age (years)	64.2 (± 6.3)	27.7 (± 4.9)	65.5 (± 5.7)	37.7 (± 6.7)	g3,g1 > g4 > g2
Age at onset (years)	57.1 (± 10.4)	25.5 (± 6.6)	not applicable	not applicable	g1 > g2
MMSE score	27.7 (± 1.9)	not applied	29.5 (± 0.6)	not applied	g3 > g1
CSF total tau protein (pg/ml)	190.6 (± 109.0)	178.0 (± 101.6)	217.0 (± 66.1)	172.2 (± 76.3)	n.sig.
CSF phosphorylated tau protein (pg/ml)	43.3 (± 17.9)	38.5 (± 14.4)	46.4 (± 8.8)	38.0 (± 11.6)	n.sig.

n.sig. not significant

in a particular patient with schizophrenia would encourage further diagnostic procedures to clarify the concomitant pathology. Furthermore, a dementia due to neurodegenerative pathology would imply with acetylcholinesterase inhibitors. Extremely high CSF tau protein levels of more than approximately 1500 pg/ml, however, are characteristic of diseases with a rapid neuronal degeneration such as Creutzfeldt-Jakob-Disease, a disorder with a variable spectrum of symptoms including delusions and hallucinations (Otto et al. 2002).

Since total tau and phospho-tau levels were demonstrated to be not influenced by neuroleptic therapy in larger samples of AD patients (Schönknecht et al. 2003, in press), potential effects of neuroleptic medication on the present results appear to be rather unlikely. However, due to the relatively small sample size, the findings of the present study need to be replicated in larger patient groups. Further studies should also consider CSF total and phospho-tau protein concentrations in schizophrenic patients differing in age at onset of the disease.

In conclusion, our study shows CSF total and phospho-tau levels not to be significantly elevated in schizophrenia. Even in old age schizophrenia, increased tau or phospho-tau levels which might have resulted from at least a concomitant neurodegenerative pathology such as AD could not be found. Taken together, our results do not exclude a progressive neurodegenerative pathology in schizophrenia per se but make it rather unlikely that the investigated schizophrenic patients suffer from an AD-related pathology or another major insult on the brain which typically would lead to increased CSF tau levels.

Acknowledgments The present study was supported in part by the Theodore and Vanda Stanley Foundation. We would like to thank Prof. Dr. H. Bardenheuer (Dept. of Anesthesiology, University of Heidelberg) for his kind cooperation.

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