

5-hydroxyindoleacetic acid and homovanillic acid concentrations in cerebrospinal fluid in patients with Alzheimer's disease, depression and mild cognitive impairment

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Abstract

In this study we investigated the cerebrospinal fluid (CSF) concentrations of 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) in Alzheimer (AD) patients (n=75), patients with mild cognitive impairment (MCI, n=9) and patients with depression (n=7). CSF HVA was significantly elevated in AD with depression (Geriatric Depression Scale, 15 point version GDS>5) in comparison to AD without depression (p<0.05, ANOVA) and CSF HVA showed a significant positive correlation with the GDS score of AD-patients (p=0.03, Spearman Rho: 0.38, Spearman Rank Correlation). In the group of AD patients CSF 5-HIAA was positively correlated with cerebrospinal fluid beta-amyloid 1-42 (Abeta42), p<0.05, Spearman Rho: 0.3, Spearman Rank Correlation, but not with CSF tau. Additionally, there was a significant positive correlation between cerebrospinal fluid 5-HIAA and HVA in the group of AD patients (p<0.0001, Rho: 0.47, Spearman Rank correlation). Neither 5-HIAA nor HVA in CSF could differentiate between mild cognitive impairment, depression and AD. The results of this study support the hypothesis that the serotonergic system plays a role in the course of AD. They further suggest an important role of dopamine metabolism in depression within AD patients.

Introduction

The central serotonergic and dopaminergic systems can be significantly altered in AD patients [Lai et al. 2002, Sjogren et. al 1998, Backman et. al, 2000, Molchan et. al, 1991]. Especially the serotonergic system seems to influence the course of AD [Lai et al. 2002]. In this study we investigated the CSF concentrations of 5-HIAA and HVA

in AD patients. These patients belong to a bigger study group that was described previously [Ganzer et al. 2003, Stuerenburg et al. 2004]. We correlated CSF 5-HIAA and HVA with the established diagnostic parameters CSF Abeta42 and CSF tau as well as with clinical scores of depression (Geriatric Depressions Scale, 15 point version).

Materials

Methods and Patients: CSF 5-HIAA, HVA and Abeta42 levels were measured in 92 patients diagnosed according to the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association) criteria. The clinical evaluation included detailed medical history, psychiatric, somatic and neurological status, neuropsychological testing, routine blood tests, an electroencephalogram, a computed tomography scan or magnetic resonance imaging. The Mini-Mental-Status examination (MMSE) test was used for staging severity of cognitive impairment and was performed prior to the start of any treatment affecting the central nervous system (e.g. acetylcholine esterase inhibitors, antidepressants or antipsychotic drugs). Depression was diagnosed with the Geriatric Depression Scale 15 (GDS 15). Lumbar puncture was performed in a standardized way using atraumatic needles with patients lying on their back for two hours before puncture. CSF samples were immediately deep frozen, routine biochemical analysis was performed as described in a previous study [Ganzer et al. 2003]. CSF 5-HIAA and CSF HVA levels were determined with electrochemical detection using HPLC [Stuerenburg and Kunze 1998, Stuerenburg and Schoser 1999, Stuerenburg et al. 2002, Stuerenburg et al. 2003].

Results

92 patients were included in the study. These 92 patients were divided into the following diagnostic groups: AD: n=43, AD with depression: n=32, mild cognitive impairment (MCI): n=7, MCI with depression: n=2, depression: n=7. The mean age was 68.1 ± 10.4 years, there were 50 female and 42 male patients. The mean MMSE score was 19.4 ± 5.4 (SD). The mean CSF 5-HIAA levels were 16.68 ± 7.5 ng/ml in AD without depression and 16.4 ± 6.1 ng/ml in AD with depression. Mean CSF 5-HIAA levels were 13.7 ± 2.3 ng/ml in the MCI-patients without depression, 12.5 ± 6.7 ng/ml in MCI patients with depression and 15.4 ± 6.9 ng/ml in patients with depression. Mean CSF HVA levels were 137.9 ± 21.3 ng/ml in AD without depression, 149 ± 27.4 ng/ml in AD with depression, 142.4 ± 2.8 ng/ml in MCI without depression 134.2 ± 24.0 in MCI with depression and 133.1 ± 24.9 ng/ml in depressive patients. In all AD patients mean CSF tau was 557.4 ± 318 pg/ml, mean CSF Abeta42 was 251 ± 61 pg/ml. The mean duration of disease was 33.8 ± 22.4 month at the time of clinical evaluation and lumbar puncture. There were no significant differences in CSF 5-HIAA concentrations between the different diagnostic groups ($p > 0.05$, ANOVA). CSF HVA was significantly elevated in AD with depression (GDS > 5) in comparison to AD without depression ($p < 0.05$, ANOVA). CSF HVA showed a significant correlation with the GDS 15 score of AD-patients ($p = 0.03$, Spearman Rho: 0.38). In all AD patients, we found a significant positive correlation between cerebrospinal fluid

5-HIAA and HVA ($p < 0.0001$, Rho: 0.47, Spearman Rank correlation), and a significant positive correlation between CSF Abeta42 and 5-HIAA ($p < 0.05$, Rho: 0.3). There was no significant correlation between CSF 5-HIAA or CSF HVA and MMSE, duration of the disease, gender, age or APOE epsilon4-allele frequency.

Conclusion

Recent studies suggested a connection between the central serotonergic function and the course of Alzheimer's disease. Lai et al. [2002] showed a negative correlation of serotonin levels in the frontal cortex with the yearly decline in the MMSE. The density of serotonin 1A receptors was positively correlated with the decline in MMSE. Lai et al. [2002] suggested that reduced serotonin levels and an increased density of serotonin 1A receptors are responsible for a faster cognitive decline in AD patients. They suggested the use of serotonin 1A antagonists as a new therapy for AD. In accordance with their findings, our study showed a significant positive correlation between CSF Abeta42 and CSF 5-HIAA. Decreased levels of CSF Abeta42 are associated with AD and the APOE epsilon4 allele, the epsilon4-allele is associated with reduced cerebrospinal fluid levels of CSF Abeta42 [Prince et al. 2004]. Additionally, a relationship between depression and ApoE epsilon4-allele in AD is discussed [Müller-Thomsen et al. 2003].

Therefore, on the basis of these results, one could hypothesize that the serotonin metabolite 5-HIAA might slow down the course of the disease or might even be useful in the prevention of the disease.

Another explanation for our findings could be that the decrease of CSF Abeta42 during the course of the disease is responsible for the decrease of CSF 5-HIAA. Sjogren et al [1998] also showed a significant decrease of 5-HIAA in CSF in AD patients in comparison to normal controls. In accordance with our findings they also found decreased CSF HVA levels, CSF 5-HIAA was significantly reduced in patients with antidepressive medication. Another study showed a decrease in CSF HVA during prolonged antidepressive medication, a normalization of CSF HVA levels was found after 30 weeks of treatment [Backman et al, 2000].

Our results support the hypothesis that there is a possible association of the serotonergic system with the course of AD, even though the CSF concentration of tau showed no correlation with the serotonin metabolites 5-HIAA or HVA or the clinical parameter MMSE. The CSF concentrations of the dopamine metabolite didn't show any correlation with the course of the disease either. However, we found elevated CSF HVA levels in AD patients with depression. Scher et al, 2003 showed that depressive patients with a former history of alcohol abuse had lower levels of CSF HVA. They also had a higher degree of lifetime aggression and more nicotine abuse than depressive patients without former alcohol abuse. Our study showed no connection between the CSF serotonergic system and depression in AD patients, but a relationship between

HVA and depression. We also found an association between 5-HIAA and Abeta42 but not with CSF tau. Neither 5 HIAA nor HVA could differentiate between mild cognitive impairment, depression or AD (with or without depression).

Our results support the hypothesis that a therapy of AD with serotonin reuptake inhibitors (SSRI) could influence the course of the disease. Our results support the hypothesis of an association between the central nervous serotonergic system with the course of AD. They also indicate an association between the central dopamin metabolism and depression in AD.

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