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LETTER TO THE EDITORS

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Neurochemical parameters in senile dementia of the Alzheimer type

A longitudinal study in four cases

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The neuronal degeneration in senile dementia of the Alzheimer type (SDAT) is accompanied by characteristic neurochemical alterations. While the main discussion focuses on the cholinergic system, changes in other transmitter systems, especially in the noradrenergic and serotonergic system, are reported (1). Moreover, a deficiency of the neuropepide somatostatin, attributable to intrinsic cortical neurons, appears to be a prominent neuropathological and neurochemical feature of SDAT. In SDAT, there exists a close association of SLI with senile plaques and tangle formation containing abnormal proteinaceous structures (2). Little is known about the intraindividual time course of neurotransmitters and neuropeptides in the cerebrospinal fluid (CSF) of patients with SDAT.

In a small longitudinal study, we investigated in four patients with SDAT somatostatin-like immunoreactivity (SLI), its molecular forms, hydroxyindoleacetic acid (HIAA) as a serotonergic marker and homovanillic acid (HVA) as a dopaminergic marker in the CSF by repeated lumbar punctures over up to 32 months.

SLI was determined using a specific antibody (K-18) which recognizes the somatostatin molecule at the ring structure. SLI was fractionated by reversed-phase HPLC using a C-18 column revealing molecular heterogeneity of SLI. HIAA and HVA were determined by HPLC and electrochemical detection. At the time of each lumbar puncture cognitive impairment was evaluated by use of the global deterioration scale of Reisberg (GDS).

1. A decrease of HIAA and HVA in the CSF of patients with SDAT was observed only over a longer duration of severest dementia (GDS 7), indicating that alterations of monoaminergic systems may be secondary and less specific than changes in cholinergic and peptidergic systems.

2. The loss of SLI was correlated with the dementia scores and the progression of cognitive impairment, and proceeded typically at an earlier stage of dementia (GDS 5-6). After separation of SLI four peaks were eluted: a first peak eluting with the void volume probably corresponding to the high molecular weight form (HMV-SST) was followed by two pronounced peaks eluting at retention times of synthetic somatostatin-25/28 (SST-25/28) and somatostatin-14 (SST-14) and by a small and variable peak coeluting with Des-ala-somatostatin (Des-ala-SST). Despite the high intraindividual and interindividual variance, our finding of qualitative and quantitative changes in the molecular pattern of SLI (increased HMV-SST and decreased SST-14) is compatible with dysregulated and/or processing of somatostatin in SDAT (3). Although it remains to be established whether these changes of SLI and its molecular forms are specific for the neuropathological processes involved in plaque and tangle formation, the determination of SLI seems to be a relevant biochemical diagnostic tool in early SDAT.

3. In cases of long-term administration of psychopharmatherapeutics, the influence, especially of neuroleptics and antidepressants on HVA, SLI and HIAA values are to be taken into consideration. In two cases the CSF values seemed not only to reflect current influences, such as stress and physical activity, but also the proceeding administration of drugs. It is known that CSF HVA levels are increased by antipsychotic agents within periods of less than 3 weeks but return to normal drug-free levels after some weeks.

4. In all cases, we observed a high intra- and interindividual variance of the CSF values. Since it is known that several factors such as sex, age, physical activity, stress and circadian fluctuations have an influence on transmitter values in the CSF, great caution should be exerted in the interpretation of CSF data. Nevertheless, the fluctuating CSF values in cases of SDAT, observed in this longitudinal study, suggest a dynamic release of neurotransmitters

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and neuromodulators from the degenerating synapses, which will lead to large variations in the intracellular space and the CSF during more active phases of degeneration. In this sense, CSF values of neurotransmitters and their metabolites could reflect the activity of the degeneration process in SDAT.

Taking into consideration the "special conditions" of the CSF, long-term study of neurochemical parameters in the CSF may be a useful complementary tool to increase diagnostic and prognostic significance and also pathophysiological meaning of dementia according to the degree of clinical impairment.

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