The urate and xanthine concentrations in the cerebrospinal fluid in patients with vascular dementia of the Binswanger type, Alzheimer type dementia, and Parkinson’s disease

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Summary. We determined the urate and xanthine concentrations in the cerebrospinal fluid (CSF) in patients with vascular dementia of the Binswanger type (VDBT), Alzheimer type dementia (ATD), and Parkinson’s disease (PD). We found that the urate concentration was significantly increased in VDBT patients, but significantly decreased in ATD patients compared with controls. The ratio of the concentrations of uric acid (U_{CSF}) to xanthine (X_{CSF}) in the CSF (U_{CSF}/X_{CSF}) had a significant correlation with the ratio of the U_{CSF} to the urate concentration in serum (U_{serum}) (U_{CSF}/U_{serum}) in ATD and PD, whereas U_{CSF}/U_{serum} increased independently of U_{CSF}/X_{CSF} in VDBT. We concluded that the significant increase in the urate concentration in VDBT is mainly due to an impairment of the blood-brain barrier (BBB), and its significant reduction in ATD may reflect impaired brain metabolism.

Keywords: Urate, xanthine, vascular dementia of the Binswanger type, Alzheimer type dementia, Parkinson’s disease, cerebrospinal fluid

Introduction

Purine nucleotides participate in a number of important biochemical processes as the monomeric units of nucleic acids, as components of energy-rich end products of most energy-releasing pathways, as the coenzymes, secondary messengers, purinergic mechanisms, and others. They are synthesized de novo, or from the degradation products of nucleic acids, and are degraded into oxypurines (hypoxanthine, xanthine) and urate. Therefore, changes in the urate and oxypurine concentrations in the cerebrospinal fluid (CSF) may provide clues for alterations of nucleotide metabolism in brain tissues. Previous studies have reported that urate and oxypurines increased in the CSF of patients with acute ischemic brain diseases (Hällgren et al., 1983), alcoholic withdrawal states (Carlsson and Dencker, 1973), and senile
dementia of Alzheimer type (SDAT) and multi-infarct dementia (Degrell and Niklasson, 1988). However, a major problem concerning the urate and oxypurine concentrations is their origins and interpretation of results obtained. It has been thought that urate in the CSF was exclusively derived from plasma, because xanthine oxidase, which catabolizes hypoxanthine to xanthine, and xanthine to urate, was absent or only present in very small amounts in the mammalian brain (Al-Khalidi and Chaglassian, 1965), and because the urate concentration in serum is about 20 times higher than in the CSF (Farstad et al., 1965). However, later studies have suggested that xanthine oxidase is present in the brain (Aoki et al., 1984; Betz, 1985). In contrast, the xanthine concentration in the CSF of healthy individuals is about 5 times higher than that in serum (Niklasson, 1983), is not profoundly influenced by the blood-brain barrier (BBB), and may reflect the intracellular nucleotide pool in the brain.

We studied the urate and xanthine concentrations in the CSF from patients with vascular dementia of the Binswanger type (VDBT), Alzheimer type dementia (ATD), and Parkinson’s disease (PD), compared with patients with multiple infarcts with preserved intelligence, and controls. To explore potential changes in brain uncleoide metabolism, and in the BBB in such diseases, we evaluated the correlation between the ratio of the urate (U_{CSF}) and xanthine (X_{CSF}) concentrations in the CSF (U_{CSF}/X_{CSF}) and the ratio of the urate concentrations in the CSF (U_{CSF}) and serum (U_{serum}) (U_{CSF}/U_{serum}), assuming that these ratios are closely related in the steady-state.

Materials and methods

Subjects

Subjects were 15 patients with VDBT (69 ± 6 years) (mean ± S.D.), 10 patients with ATD (68 ± 8 years), 11 patients with Parkinson’s disease (67 ± 6 years), 6 patients with multi-infarcts with normal intelligence (70 ± 6 years), and 14 controls (68 ± 6 years). The duration of the diseases was 3.8 ± 4.1 years for VDBT, 3.9 ± 2.1 years for ATD, 2.4 ± 0.8 years for PD, and 3.8 ± 2.1 years for multi-infarcts unassociated with dementia. Control CSF samples were obtained from neurologically normal patients who underwent hemorrhoidectomy at the time of lumbar anesthesia before surgery. All patients were admitted to the hospital, placed on the same standard diet, and were drug-free for at least 2 weeks. Informed consent was obtained from all patients prior to this study.

Diagnostic criteria

The diagnosis of ATD and VDBT was made according to DSM-III-R (American Psychiatric Association, 1987), Hachinski’s Ischemic Score (Hachinski et al., 1975), the criteria of the NINCDS-ADRDA Work Group (McKhann et al., 1984), and CT and MRI findings. All patients with VDBT had a diffuse and extensive low density area on CT scans, and diffuse high intensity area on T2-weighted MRI in the cerebral white matter (leukoaraiosis; Hachinski et al., 1987), not associated with infarcts greater than 3 cm in diameter. We strictly excluded patients having vascular lesions for the diagnosis of ATD. However, we were not able to exclude the possibility that some of our patients diagnosed as having VDBT may actually have had mixed dementia (VDBT