J Neural Transm [P-D Sect] (1992) 4: 69–77

Journal of Neural Transmission

Concentrations of monoamines and their metabolites in the cerebrospinal fluid from patients with senile dementia of the Alzheimer type and vascular dementia of the Binswanger type

H. Tohgi, M. Ueno, T. Abe, S. Takahashi, and **Y. Nozaki**

Department of Neurology, Iwate Medical University, Morioka, Japan

Accepted July 25, 1991

Summary. We measured the concentrations of total (conjugated and unconjugated) monoamines (dopamine, DA; norepinephrine, NE) and monoamine metabolites (homovanillic acid, HVA; 3-methoxy-4-hydroxyphenyleneglycol, MHPG; 5-hydroxyindoleacetic acid, 5-HIAA) in the cerebrospinal fluid (CSF), using HPLC-ECD in 11 patients with Alzheimer's disease (AD) or senile dementia of the Alzheimer type (SDAT), 17 patients with vascular dementia of the Binswanger type (VDBT), and 15 controls. In AD/SDAT, there was a significant decrease in the DA concentration and a significant increase in the MHPG concentration. The average NE concentration was not altered, but significantly increased with the progression of intellectual disability. There were no significant changes in HVA and 5-HIAA concentrations. Patients with VDBT showed a significant increase in the DA concentration and a significant decrease in HVA and 5-HIAA concentrations. The DA concentrations increased significantly with the progression of dementia and ventricular enlargement. These results indicate that the noradrenergic and dopaminergic system in particular are altered in AD/SDAT, while the dopaminergic and serotonergic systems are mainly involved in VDBT.

Keywords: Dopamine, norepinephrine, cerebrospinal fluid, senile dementia of the Alzheimer type, vascular dementia of the Binswanger type.

Introduction

Many studies have reported changes in the monoamine concentrations in autopsy brains (Adolfsson et al., 1979; Carlsson, 1983; Cross et al., 1983; Mann et al., 1982; Winblad et al., 1982) and the cerebrospinal fluid (CSF) (Argentiero and Tavolato, 1980; Bareggi et al., 1982; Gottfries et al., 1969, 1970; Guard et al., 1976; Palmer et al., 1984; Raskind et al., 1984; Soininen et al., 1981; Wood et al., 1982) from patients with Alzheimer's disease (AD) or senile dementia of

the Alzheimer type (SDAT). While the monoamine concentrations in the autopsy brains indicate the monoaminergic activity at the end stage of the disease, those in the CSF clearly reflect the monoaminergic activities in vivo (Wester et al., 1990), and may be possibly correlated with the severity of dementia. Although the monoamine concentration in the CSF are affected by many factors, and hence has a limited value, a postmortem study has shown that central monoaminergic activity is well reflected in the concentrations of monoamines and their metabolites in the CSF (Wester et al., 1990). Since previous studies on monoamine concentrations in the CSF have been performed mainly on their metabolites (3-methoxy-4-hydroxyphenyleneglycol, MHPG; homovanillic acid, HVA) (Argentiero and Tavolato, 1980; Bareggi et al., 1982; Bowen et al., 1981; Gottfries et al., 1969, 1970; Guard et al., 1976; Palmer et al., 1984; Raskind et al., 1984; Soininen et al., 1981; Wood et al., 1982), simultaneous measurements of monoamines (dopamine, DA; norepinephrine, NE; epinephrine, EP) and their metabolites would contribute to our better understanding of monoamine metabolism in the CSF.

On the other hand, there are only limited data on monoamine concentrations in the CSF in vascular dementia (Smirne et al., 1985), another frequent disease in the elderly presenting dementia. Since multi-infarct dementia (MID) is characterized by a random, multifocal distribution of infarcts, transmitter abnormalities may be heterogeneous among MID patients. In this study, we selected patients with vascular dementia of the Binswanger type (VDBT) which is believed to be a relatively homogeneous group. Although the definition of VDBT is a matter of some debate, we identified patients with VDBT on the basis of clinical features and ischemic periventricular leukoencephalopathy (Román, 1987) demonstrated by computed tomography (CT) and magnetic resonance imaging (MRI). An autopsy study has demonstrated a close (90%) correlation between the white matter low attenuation and the periventricular ischemic white matter changes in the brains (Lotz et al., 1986). We therefore studied the concentrations of NE, DA, MHPG, HVA, and 5-HIAA in the CSF from patients with AD/SDAT and VDBT, and their correlations with the severity of dementia.

Material and methods

Subjects

Subjects were 11 patients with AD/SDAT (70.8 ± 8.2 years), 17 patients with VDBT (72.1 ± 8.3 years), and 15 controls (69.1 ± 9.5 years). The average duration of illness was 3.8 ± 2.3 years for patients with AD/SDAT and 3.6 ± 1.6 years for patients with VDBT. The diagnosis of AD/SDAT and VDBT was made according to the DSM-III-R (American Psychiatric Association, 1987), Hachinski's Ischemic Score (Hachinski et al., 1975), and the criteria of the NINCDS-ADRDA Work Group (McKhann et al., 1984), and CT and MRI findings.

Diagnostic criteria

We diagnosed patients as having VDBT if they fulfilled all the following criteria: (1) clinical characteristics of vascular dementia [DSM-III-R (American Psychiatric Association, 1987)]

and Hachinski's Ischemic Score (Hachinski et al., 1975); (2) absence of infarcts which alone may produce dementia: large infarcts (greater than 3 cm in diameter) or infarcts of the thalamus, hippocampus or the cingulate gyrus; (3) presence of an extensive area of low density in the white matter on CT scans, usually associated with multiple lacunes in the basal grey matter; and (4) absence of other etiological conditions which may cause diffuse white matter changes (e.g., intoxication or inflammation). The Hachinski's ischemic scores were 2.2 ± 1.2 for AD/SDAT patients and 11.1 ± 2.3 for VDBT patients. The controls consisted of patients with tension headache.

Intellectual ability

The intellectual ability was assessed by Hasegawa's dementia scale (HDS) (Hasegawa et al., 1974), which is similar to the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), consisting of tests for memory, orientation, general knowledge, and calculation (range = 0–32.5 points: normal, 31.0–32.5; mildly impaired, 22.0–30.5; moderately impaired, 10.5–21.5; and severely impaired, 0–10.0). The estimates of the HDS were significantly correlated with estimates of MMSE ($r = 0.88$, $p < 0.01$, $n = 24$). The average scores of the HDS were 8.8 ± 7.1 for AD/SDAT patients, and 9.4 ± 5.1 for VDBT patients. There was no correlation between the scores of HDS and the age of patients. Bed-ridden patients were excluded. All patients were admitted to the hospital, placed on the same standard diet, and were drug-free for at least two weeks. Informed consent was obtained from all patients and their relatives.

CSF analysis

Lumbar cerebrospinal fluid was obtained with subjects in the lateral position between 9 and 10 am after an overnight fast and bed rest for 12 h. An initial 3 ml of CSF was used for routine examination, and then additional 2 ml of CSF was collected and stored at −80 °C for monoamine analysis.

The total of free and conjugated monoamines were determined essentially according to the method described by Tyce et al. (1985) with some modifications. After the addition of 100 µl of 3 M perchloric acid, 10 µl of 25 mM sodium thiosulfate, and 20 µl of 40 ng/ml N-methyl dopamine (NMDA) as an internal standard, the aliquot was boiled for 30 min to hydrolyze conjugated amines. The aliquot was titrated to pH 7.5 by 100 µl of 1 M K_2HPO_4 containing 10% EDTA (pH 7.50) and 200 µl of 1 M K_2CO_3, and centrifugated at 13,000 G for 2 minutes. The supernatants were added to 10 mg of boric acid gel and mixed for 30 minutes. After centrifugation for 2 minutes, the supernatants were discarded. The borate gel was washed two times with distilled water, and then 100 ml of 0.75 M acetic acid was added, and the resulting solution was mixed for 10 sec.

The 100 µl of the extracts were applied to columns (Shimipack CLS-ODS: 0.15 m × 60 ∅) of HPLC (Shimadzu LC-6 A)) with an electrochemical detector (Model 5100 A, Niko Bioscience). The mobile phase was 0.1 M sodium citrate buffer (pH 5.0). The temperature was kept at 45 °C. The electrode potentials were maintained at 0.33 V for the guard cell, -0.10 V for detector I and -0.30 V for detector II. DA, NE, and EP were oxidized by detector II. Recoveries of authentic standard compounds were 80–85% for NE, 85–90% for EP, and 70–75% for DA. Coefficients of variation were 5–6.5% (n = 10). HVA, MHPG, and 5-HIAA concentrations were measured by injecting 40 µl of cerebrospinal fluid samples directly to the HPLC system. The sensitivity of the assay was less than 10 pg/ml.

Determination of ventricular dilatation

The degree of ventricular dilatation was estimated by the cella media index (CMI: the quotient of the biparietal diameter and the largest external distance of the lateral ventricle

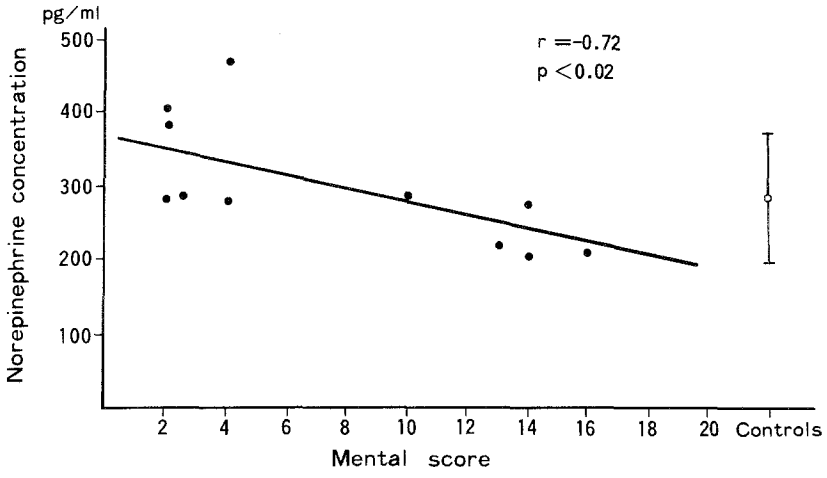

Fig. 1. Correlation between mental scores and norepinephrine concentrations in the cerebrospinal fluid from patients with senile dementia of the Alzheimer type

in the region of the cella media) (Meese et al., 1976). Smaller CMI values signify severer degrees of ventricular dilatation and parenchymal atrophy.

Statistics

The inter-group differences of mean values were analysed by one-way analyses of variance. The correlation coefficients were calculated by the Pearson product-moment correlation.

Results

In patients with AD/SDAT, the MHPG concentrations increased significantly compared with the controls ($p < 0.05$), while the NE concentrations were unchanged (Table 1). However, the NE concentrations had a significantly negative correlation with intellectual ability ($r = -0.72$, $p < 0.02$) (Fig. 1): they were within the lower normal range in the mild stage of dementia and increased slightly in the advanced stage. The DA concentrations decreased significantly compared with controls ($p < 0.05$) (Table 1). There was no significant difference in monoamine concentrations between patients younger than 65 (4 cases; DA, 0.513 ± 0.129 ng/ml; NE, 0.315 ± 0.069 ng/ml; EP, 0.059 ± 0.010 ng/ml) and patients aged 65 or more (7 cases; DA, 0.544 ± 0.159 ng/ml; NE, 0.278 ± 0.099 ng/ml; EP, 0.046 ± 0.020 ng/ml). There were no significant changes in HVA and 5-HIAA concentrations.

The patients with VDBT showed a significant increase in the DA concentrations ($p < 0.01$), and a significant reduction in the HVA concentrations ($p < 0.05$), and the 5-HIAA concentrations ($p < 0.01$) (Table 1). The DA concentrations were higher than the control values in the mild stage and displayed the tendency to increase further with progression of dementia, though the changes were not significant (Fig. 2). The NE, EP, and MHPG concentrations did not change significantly.

Table 1. The concentrations (ng/ml) of monoamines and their metabolites in the CSF from patients with senile dementia of the Alzheimer type (SDAT) and vascular dementia of the Binswanger type (VDBT) compared with controls. Values are means ± S.D.

	Controls	SDAT	VDBT
Norepinephrine (NE)	0.33 ± 0.12	0.29 ± 0.09	0.38 ± 0.13
MHPG	8.24 ± 2.29	11.6 ± 4.09*	8.56 ± 3.47
Dopamine (DA)	0.66 ± 0.20	0.53 ± 0.14*	1.11 ± 0.21**
HVA	29.6 ± 11.0	29.5 ± 16.4	20.7 ± 9.3*
Epinephrine	0.06 ± 0.04	0.05 ± 0.04	0.06 ± 0.04
5HIAA	29.0 ± 17.4	29.3 ± 11.2	19.9 ± 6.19**

Statistics: ANOVA: * $p < 0.05$, ** $p < 0.01$ compared with controls

The CMI had a significantly negative correlation with DA concentrations in patients with SDAT ($r = -0.76$, $p < 0.02$). The concentrations of other monoamnines did not show any correlation with CMI, indicating that there was no "dilution effect" associated with ventricular dilatation. In all study groups, there were no differences in monoamine concentrations between males and females.

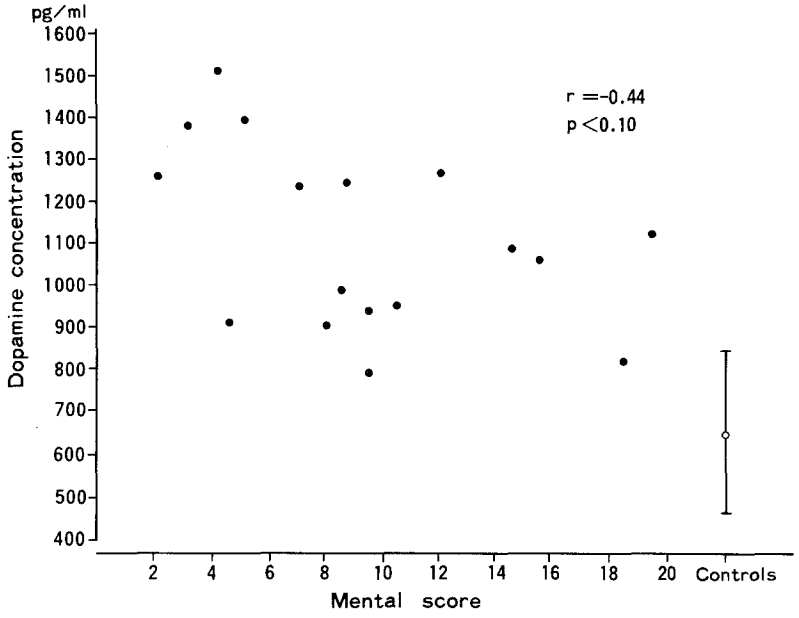

Fig. 2. Correlation between mental scores and dopamine concentrations in the cerebrospinal fluid from patients with vascular dementia of the Binswanger type. No significant changes were found in DA concentrations with progression of dementia

Discussion

Our main findings are (1) that the noradrenergic and dopaminergic systems are particularly altered in AD/SDAT; and (2) that the dopaminergic and serotonergic systems are mainly involved in VDBT. None of the substances measured are known to cross the blood-brain or blood-CSF barriers (Bartholini et al., 1966; Kopin et al., 1983) except for MHPG, which has been reported to diffuse through the blood-brain and blood-CSF barriers (Kopin et al., 1983). However, it has been reported that the MHPG concentration in the CSF had the significant positive correlation with that in some brain areas (Wester et al., 1990).

We found that the NE concentrations in the CSF from patients with AD/SDAT increased stage-dependently, whereas MHPG concentrations increased significantly with no correlation with the severity of dementia. Previous studies on the autopsy brains from patients with SDAT have demonstrated loss of noradrenergic neurons in the locus ceruleus (Mann et al., 1980; Tomlinson et al., 1981), a decrease in NE content (Adolfsson et al., 1979; Mann et al., 1982), and dopamine β-hydroxylase activity of the cerebral cortex (Cross et al., 1981). However, other studies have demonstrated elevated MHPG concentrations in autopsy brains (Winblad et al., 1982), and increased NE and MHPG levels in the CSF from advanced cases with AD (Raskind et al., 1984). It is difficult at present to explain the discrepancy between the increase in NE and MHPG concentrations in the CSF and the reported dercrease in NE concentrations in autopsy brains. One possible explanation is that NE receptors may be hyperactive to compensate for the decreased NE release from noradrenergic neuron terminals, and thus leads to an enhanced metabolism of NE and the elevation of MHPG levels.

The significant decrease in the DA concentration in AD/SDAT is consistent with previous findings in autopsy brains (Adolfsson et al., 1979). The negative correlation between the DA level and CMI in AD/SDAT may be due to the progressive deterioration of the postsynaptic DA metabolism with progression of dementia. Alternatively, some of the advanced cases with AD/SDAT may have ischemic lesions smaller than the limits of CT resolution. Although the unaltered HVA level as shown in our results has been reported in some previous studies for the CSF (Adolfsson et al., 1979; Wood et al., 1982) and autopsy brains (Cross et al., 1983), many other investigators have reported the reduction in the HVA and 5-HIAA concentrations in the CSF from AD/SDAT patients (Argentiero and Tavolato, 1980; Bareggi et al., 1982; Gottfries et al., 1969, 1970; Guard et al., 1976; Palmer et al., 1984), and their correlation with the degree of dementia (Bareggi et al., 1982; Gottfries et al., 1970; Parnetti et al., 1987; Bråne et al., 1989). The discrepancy between these reports and the present results may be mainly because we did not include severe patients with mental scores of 0 or 1, and suggest that impairments of the DA system are reflected earlier in DA than in HVA concentrations.

The decrease in the HVA concentrations in our VDBT patients is consistent

with previous CSF findings in multi-infarct dementia (Smirne et al., 1985); however, we found a significant increase in the DA concentration which seemed to parallel the severity of dementia and ventricular enlargement. Experimental studies on acute cerebral ischemia or hypoxia have shown a remarkable increase in extracellular DA associated with unaltered DA metabolites, the decrease in 3, 4-dihydroxyphenylacetic acid (DOPAC) in the striatum (Slivka et al., 1988), the increased activity of tyrosine hydroxylase (Siesjö, 1978), and the inhibition of monoamine reuptake and oxidative deamination (Pastuszko et al.,1982; Weinberger and Cohen, 1982). Although changes in the dopaminergic system during chronic ischemia are unknown, our findings suggest an enhanced release, and a decreased reuptake and metabolism of DA due to hypoxia in VDBT.

The present results suggest both presynaptic and postsynaptic abnormalities in different monoaminergic systems of the dementias. The dopaminergic axons from the ventral tegmental area and the substantia nigra project preferentially to the prefrontal and medial frontal cingulate cortex (Björklund et al., 1978), and appear to be essential for normal frontal function, whereas noradrenergic fibers innervate much wider areas, particularly the parietal somatosensory cortex (Molliver et al., 1982). Neuropathological (Brun and Gustafson, 1976) and brain imaging findings (Jagust et al., 1987) and psychometric testings (Christensen, 1990) have demonstrated the early and severe parieto-temporal cortical affection in AD/SDAT, as compared with a preferential involvement of the frontal area in vascular dementia (Jagust et al., 1987; Wolfe et al., 1990). The present results, therefore, suggest a possible correlation between transmitter abnormalities, neuropathological and neuroimaging findings, and neuropsychological features.

Acknowledgements

We thank Miss Y. Oda for technical assistance, and Dr. P. Langman and Miss M. Yamazaki for preparation of the manuscript. This study was supported in part by a grant-in-aid of the Ministry of Education, Science and Culture, Japan.

References

Adolfsson R, Gottfries CG, Ross BE, Winblad B (1979) Changes in the brain catecholamines in patients with dementia of Alzheimer type. Br J Psychiatry 135: 216–223

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders, 3 rd ed (revised). APA, Washington DC, pp 21–23

Argentiero V, Tavolato B (1980) Dopamine (DA) and serotonin metabolic levels in the cerebrospinal fluid (CSF) in Alzheimer's presenile dementia under basic conditions and after stimulation with cerebral cortex phospholipids (BC-PL). J Neurol 224: 53–58

Bareggi SR, Franceschi M, Bonini L, Zecca L, Smirne S (1982) Decreased CSF concentrations of homovanillic acid and α-aminobutyric acid in Alzheimer's disease. Age- or disease-related modifications? Arch Neurol 39: 709–712

Bartholini G, Pletscher A, Tissot R (1966) On the origin of homovanillic acid in the cerebrospinal fluid. Experientia 22: 609–610

Björklund A, Divac I, Lindvall O (1978) Regional distribution of catecholamines in monkey cerebral cortex, evidence for a dopaminergic innervation of the primate prefrontal cortex. Neurosci Lett 7: 115–119

Bowen DD, Sims NR, Benton JS, Curzon G, Davison AN (1981) Treatment of Alzheimer's disease: a cautionary note. N Engl J Med 305: 1016

Bråne G, Gottfries CG, Blennow K, Karlsson I, Lekman A, Parnetti L, Svennerholm L, Wallin A (1989) Monoamine metabolites in cerebrospinal fluid and behavioral ratings in patients with early and late onset Alzheimer dementia. Alzheimer Disease and Associated Disorders 3: 148–156

Brun A, Gustafson L (1976) Distribution of cerebral degeneration in Alzheimer's disease. A clinicopathological study. Arch Psychiat Nervenkr 223: 15–33

Carlsson A (1983) Changes in neurotransmitter systems in the aging brain and in Alzheimer's disease. In: Reisberg B (ed) Alzheimer's disease. Macmillan, New York, pp 100–106

Christensen A-L (1990) Neuropsychological approach to Alzheimer's dementia. In: Hasegawa K, Homma A (eds) Psychogeriatrics. Biomedical and social advances. Excerpta Medica, Amsterdam Princetom Hong Kong Tokyo Sydney, pp 169–174

Cross AJ, Grow TJ, Perry EK, Perry RH, Blessed G, Tomlinson BE (1981) Reduced dopamine-beta-hydroxylase activity in Alzheimer's disease. Br Med J 282: 93–94

Cross AJ, Grow TJ, Johnson JA, Joseph MH, Perry EK, Perry RH, Blessed G, Tomlinson BE (1983) Monoamine metabolism in senile dementia of Alzheimer type. J Neurol Sci 60: 383–392

Folstein MF, Folstein SE, McHugh PR (1975) "Mini-Mental State". A practical method of grading. The cognitive state of patients for the clinician. J Psychiatr Res 12: 189–198

Gottfries CG, Gottfries I, Roos BE (1969) Homovanillic acid and 5-hydroxyindoleactic acid in the cerebrospinal fluid of patients with senile dementia, presenile dementia and parkinsonism. J Neurochem 16: 1341–1345

Gottfries CG, Gottfries I, Roos BE (1970) Homovanillic acid and 5-hydroxyindoleacetic acid cerebrospinal fluid related to rated mental and motor impairment in senile and presenile dementia. Acta Psychiatr Scand 46: 99–105

Guard O, Renaud B, Chazot G (1976) Métabolisme cérébral de la dopamine et de la sérotonine au cours des maladies d'Alzheimer et de Pick. Etude dynamique par le test au probénécide. Encephale 2: 293–303

Hachinski VC, Iliff LD, Zilhka E, Du Boulay GH, McAllister VL, Marshall J, Ross Russell RW, Symon L (1975) Cerebral blood flow in dementia. Arch Neurol 32: 632–637

Hasegawa K, Inoue K, Moriya K (1974) An investigation of dementia rating scale for the elderly. Clin Psychiatry 16: 965–969 (in Japanese)

Jagust WJ, Budinger TF, Reed BR (1987) The diagnosis of dementia with single photon emission computed tomography. Arch Neurol 44: 258–262

Kopin IJ, Gordon EK, Jimerson DC, Polinsky RJ (1983) Relation between plasma and cerebrospinal fluid levels of 3-methoxy-4-hydroxyphenylglycol. Science 219: 73–75

Lotz PR, Ballinger WE Jr, Quisling RG (1986) Subcortical arteriosclerotic encephalopathy: CT spectrum and pathologic correlation. AJNR 7: 817–822

Mann DMA, Lincoln J, Yates PO, Stamp JE, Toper S (1980) Changes in the monoamine containing neurons of the human CNS in senile dementia. Br J Psychiatry 136: 533–541

Mann DMA, Yates PO, Hawkes J (1982) The noradrenergic system in Alzheimer and multi-infarct dementias. J Neurol Neurosurg Psychiatry 45: 113–119

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34: 939–944

Meese W, Lanksch W, Wende S (1976) Cerebral atrophy and computerized tomography – Aspects of a qualitative and quantitative analysis. In: Lanksch W, Kazner E

(eds) Cranial computerized tomography. Springer, Berlin Heidelberg New York, pp 222–232

Molliver ME, Grzanna R, Lidov HGW, Morrison JH, Olschowka JA (1982) Monoamine systems in the cerebral cortex. In: Chan-Palay V, Palay B (eds) Cytochemical methods in neuroanatomy. Alan R Liss, New York, pp 255–277

Palmer AM, Sims NR, Bowen DM, Neary D, Palo J, Wikstrom J, Davison AN (1984) Monoamine metabolite concentrations in lumbar cerebrospinal fluid of patients with histologically verified Alzheimer's dementia. J Neurol Neurosurg Psychiatry 47: 481–484

Parnetti L, Gottfries J, Karlsson I, Långström G, Gottfries C-G, Svennerholm L (1987) Monoamines and their metabolites in cerebrospinal fluid of patients with senile dementia of Alzheimer type using high performance liquid chromatography and gas chromatography-mass spectrometry. Acta Psychiatr Scand 75: 542–548

Pastuszko A, Wilson DF, Erecińska M (1982) Neurotransmitter metabolism in rat brain synaptosomes: effect of anoxia and pH. J Neurochem 38: 1657–1667

Raskind MA, Peskind ER, Halter JB, Jimerson DC (1984) Norepinephrine and MHPG levels in CSF and plasma in Alzheimer's disease. Arch Gen Psychiatry 41: 343–346

Román GC (1987) Senile dementia of the Binswanger type. A vascular form of dementia in the elderly. JAMA 258: 1782–1788

Siesjö BK (1978) Brain energy metabolism and catecholaminergic activity in hypoxia, hypercapnia and ischemia. J Neural Transm 14[Suppl]: 17–22

Slivka A, Brannan TS, Weinberger J, Knott PJ, Cohen G (1988) Increase in extracellular dopamine in the striatum during cerebral ischemia: a study utilizing cerebral microdialysis. J Neurochem 50: 1714–1718

Smirne S, Franceschi M, Truci G, Camerlingo M, Pirola R, Ferini-Strambi L, Bareggi SR (1985) Homovanillic acid and 5-hydroxyindoleacetic acid modifications in CSF of patients with stroke and multi-infarct dementia. Stroke 16: 1003–1005

Soininen H, MacDonald E, Rekonen M, Riekkinen PJ (1981) Homovanillic acid and 5-hydroxyindoleacetic acid levels in cerebrospinal fluid of patients with senile dementia of Alzheimer type. Acta Neurol Scand 64: 101–107

Tomlinson BE, Irving D, Blessed G (1981) Cell loss in the locus coeruleus in senile dementia of Alzheimer type. J Neurol Sci 49: 419–428

Tyce GM, Rorie DK, Byer DE, Danielson DR (1985) Free and conjugated amines in human lumbar cerebrospinal fluid. J Neurochem 49: 322–324

Weinberger J, Cohen G (1982) The differential effect of ischemia on the active uptake of dopamine, γ-aminobutyric acid, and glutamate by brain synaptosomes. J Neurochem 38: 963–968

Wester P, Bergström U, Eriksson A, Gezelius C, Hardy J, Winblad B (1990) Ventricular cerebrospinal fluid monoamine transmitter and metabolite concentrations reflect human brain neurochemistry in autopsy cases. J Neurochem 54: 1148–1156

Winblad B, Adolfsson R, Carlsson A, Gottfries CG (1982) Biogenic amines in brains of patients with Alzheimer's disease. In: Corkin S, Davis KL, Growdon JH, Usolin E, Wurtman RJ (eds) Alzheimer's disease: a report of progress in research. Raven Press, New York, pp 25–33

Wolfe N, Linn R, Babikian VL, Knoefel JE, Albert ML (1990) Frontal systems impairment following multiple lacunar infarcts. Arch Neurol 47: 129–132

Wood PL, Etienne P, Lal S, Gauthier S, Cajal S, Nair NPV (1982) Reduced lumbar CSF somatostantin levels in Alzheimer's disease. Life Sci 31: 2073–2079

Authors' address: Dr. H. Toghi, Department of Neurology, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020, Japan.

Received February 28, 1991