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A long-term follow-up study of cerebrospinal fluid 5-hydroxyindoleacetic acid in delirium

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Abstract Cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) was determined for elderly delirious patients during the acute stage and after a 1-year follow-up period, and the 5-HIAA levels were compared with age-equivalent controls. As compared with the controls, the 5-HIAA levels were significantly higher at the beginning of the index admission in patients with multi-infarct dementia and patients with no apparent CNS disease. The 5-HIAA levels were also higher in the latter subgroup in the 1-year sampling, but no other differences between delirious patients and controls were observed. The one-way procedure showed no differences between the subgroup means of delirious patients when divided according to the severity of cognitive decline or type of delirium in any of the samples. The 5-HIAA levels measured during the index admission correlated with the length of life after delirium suggesting that serotonergic dysfunction may have prognostic significance in delirious patients.

Key words Cerebrospinal fluid · delirium · dementia 5-hydroxyindoleacetic acid · serotonin

Introduction

Delirium is a common problem among the hospitalized elderly (Trzepacz et al. 1985; Levkoff et al. 1992). The essential features of delirium include global cognitive impairment, i.e. concurrent disorders of memory, thinking, orientation, and perception; disturbances of attention and of the sleep-wake cycle; and increased or decreased psychomotor behavior. Its course is characterized by rapid onset, relatively brief duration, and fluctuations in the severity of the disturbance over the course of a day (Lipowski 1983). Despite the varied etiology of delirium its clinical consequences are relatively stereotyped, which suggests that the diverse insults that cause delirium may act by a common metabolic and cellular pathway (Mesulam 1986; Gibson et al. 1991).

Through its widespread projections to the cortex and various limbic structures, the serotonergic (5-HT) system is involved in the regulation of a wide variety of physiologic functions. Investigations have suggested the involvement of 5-HT-systems in mood disorders, anxiety disorders, schizophrenia, Alzheimer's disease, appetite control, impulse control, self-destructive and violent behaviors, alcoholism, and obsessive-compulsive disorder (van Praag and de Haan 1979; Soininen et al. 1981).

Approaches to study the serotonin system include measurement of cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA), the main metabolite of serotonin. In addition, neuroendocrine challenge tests using a variety of precursors and direct serotonin agonists, serotonin reuptake inhibitors, and serotonin releasing agents have also been employed. As involvement of serotonergic neurons may be related to the affective and cognitive symptoms related to delirium, we decided to investigate whether CSF 5-HIAA as a serotonergic marker is affected in an etiologically heterogeneous group of delirious patients. We also studied whether this change is related to the degree of congitive deterioration, the type of delirium or the type of basic central nervous system disease. The results were obtained through a three-fold sampling of CSF: at entry into the study, 2 weeks after entry, and 1 year after entry.

Methods

Subjects

The CSF 5-HIAA was initially determined for 69 elderly patients (29 males, 40 females, mean age ± S.D. 74.8 ± 6.4 years, range 60–88 years) who were collected as previously described for our

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Table 1 Putative etiologies of delirium (n = 69)

	n
Stroke	14
Infection	9
Metabolic disorders	9
Epileptic fit	6
Adverse drug reactions	6
Life change in a deeply demented patient	6
Myocardial infarction or insufficiency	4
Extracranial carcinoma	4
Functional psychosis	3
Subdural hematoma	2
Intracerebral hemorrhage	2
Trauma	2
Cerebral tumor	1
Aneurysm of the basilar artery and hydrocephalus	1

prospective study on delirium (Koponen and Riekkinen, 1993). Patients with alcohol-related delirium were excluded, but all other delirious patients meeting the DSM-III criteria for delirium (APA, 1980) were consecutively included. The study design was approved by the Ethics Committee, and informed consent was obtained from all subjects or from the patient's family or legal guardian when necessary.

Evaluation of the putative CNS disease and the most important triggering factor for delirium in each patient was based on the patient's history, medical, neurological, and psychiatric examinations, and laboratory results including CT and EEG. The final diagnostic grouping was carried out according to the criteria of the DSM-III for multi-infarct dementia (MID), NINCDS-ADRDA (McKhann et al. 1984) for Alzheimer's disease (AD), and Hoehn and Yahr (1967) for Parkinson's disease (PD). In addition to the type of basic CNS disease, the delirious patients were divided into subgroups according to the degree of cognitive decline during acute delirium. Patients with mild cognitive decline scored from 21 to 24 on the Mini-Mental State Examination (MMSE; Folstein et al. 1975), moderate 11–20 and severe 0–10 (Duara et al. 1986). At the acute stage, delirious patients were also divided into subgroups with hyperactive, mixed or silent delirium on the basis of clinical symptoms (Lipowski 1980). The triggering factors for delirium were heterogeneous, but usually a stroke, infection, epileptic fit or metabolic encephalopathy was encountered (Table 1).

Delirium in our etiologically heterogeneous patient group lasted 19.5 ± 15.4 days and treatment in a psychiatric hospital 30.4 ± 20.5 days. 1 year after the index admission, the patients were again invited for a short hospital stay during which the CSF examinations and clinical ratings were repeated. 75% (33 out of 44) of the patients still alive participated in the 1-year follow-up visit. During the follow-up, a declining course in the cognitive functions was evident, as estimated by MMSE (Table 2). The death rate among our delirious patients is based on a follow-up period of 4 years.

Four patients died during the index admission and 42 during the whole 4-year follow-up period, which raised the overall death rate to 66%. Autopsies, together with CNS histology, were performed in seven cases, resulting in a histological diagnosis that was in accordance with the clinical life-time diagnosis in all cases (four patients with vascular brain disease, two patients with Alzheimer's disease, and one patient with no CNS disease).

Controls

The control group consisted of elderly subjects who participated in the normal aging study at Kuopio University Hospital (n = 13, 5 males, 8 females, mean age ± S.D. 72.4 ± 8.2 years). The sex distribution or mean age of the control group did not differ from those of the delirious patients. The controls lived independently at home, used no CNS-active drugs and had no history of neurological or psychiatric disorders, and showed no signs of dementia in the neuropsychological examination.

Lumbar punctures

The CSF sampling was performed in the morning at bed rest after an overnight fast. The first sampling was carried out on the first working day after the index admission; the second, 2 weeks after the beginning of the index admission; and the third, 1 year after the index admission. The first CSF aliquot (2 ml) was used for routine measurements. The next 10 ml was immediately divided into ten 1-ml portions, chilled on dry ice and frozen at -70° C until assayed.

Determination of CSF 5-hydroxyindoleacetic acid

CSF 5-HIAA was measured with HPLC using amperometric detection. After deproteinization with perchloric acid containing internal standard (3-fluoro-4-hydroxyphenylacetic acid, 800 pmol/l), the CSF samples were injected into a Nova Pak C18 column. The mobile phase consisted of a mixture of 0.1 *M* Na-acetate with 0.01 *M* citric acid and 0.25 m*M* Na2EDTA and methanol (97:3) (pH 4.85). Intra-assay and interassay coefficients of variation were 6.9 and 9.1 per cent (Jolkkonen et al. 1987).

Statistical analysis

Means and standard deviations were computed for parametric variables derived from the entire delirious patient group and from the previously mentioned subgroups. Data gathered during the index admission and follow-up were compared using Student's paired-sample or two-sample t-test. The subgroup means were compared using one-way analysis of variance followed by Student-Newman-Keul's range statistics. Correlations between the 5-HIAA concentration, MMSE score and neuroleptic dose were calculated using Pearson's correlation technique. Analysis of covariation between the CSF 5-HIAA levels and life span after the onset of delirium was carried out by using the Cox proportional hazards model.

Results

As compared with the controls, the 5-HIAA levels were significantly higher at the beginning of the index admission in patients with multi-infarct dementia and patients with no apparent CNS disease. The 5-HIAA levels were also higher in the latter subgroup in the 1-year sampling, but no other differences were observed (Table 2). The one-way procedure showed no differences between the subgroup means of delirious patients when divided according to the severity of cognitive decline or type of delirium in any of the samples.

All patients met the DSM-III criteria for delirium during the first lumbar puncture, 14 patients during the second, and none during the third CSF sampling. The paired-sample t-test showed no difference between the 5-HIAA levels of the first and second CSF sample (162.9 ± 82.6 versus 161.9 ± 121.9 nmol/l) in patients whose delirium abated during the first 2 weeks. In the second sample, the CSF 5-HIAA concentrations did not differ between recovered and still delirious patients (161.9 ± 121.2 versus

Table 2 CSF 5-HIAA concentrations in delirious patients and controls [*5-HIAA1* CSF hydroxyindoleacetic acid (nmol/l; mean ± SD) at the beginning of the index admission, *5-HIAA2* CSF hydroxyindoleacetic acid 2 weeks after the beginning of the index admission, *5-HIAA3* CSF hydroxyindoleacetic acid 1 year after the beginning of the index admission, *n* number of patients, *MID* multi-infarct dementia patients, *AD* Alzheimer patients, *PD* Parkinsonian patients, *NO* patients with no apparent CNS disease, *MMSE1* Mini-Mental State Examination score at the beginning of the index admission, *MMSE2* Mini-Mental State Examination 2 weeks after the beginning of the index admission, *MMSE3* Mini-Mental State Examination score 1 year after the beginning of the index admission]. Significance of 5 HIAA concentration differences between delirious patient subgroups and controls (two-tailed *t*-test): * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

	Type of CNS disease				
	MID	AD	PD	NO	ALL
5-HIAA1	174.6 ± 87.7*	173.6 ± 238.0	150.1 ± 56.8	168.9 ± 56.9*	172.3 ± 125.8
MMSE1	9.9 ± 5.4	7.6 ± 6.9	6.0 ± 6.2	12.2 ± 9.1	9.7 ± 6.6
n	39	14	3	13	69
5HIAA2	190.9 ± 137.4	101.6 ± 49.2	131.6 ± 31.3	154.6 ± 50.3	165.0 ± 117.1
MMSE2	14.0 ± 6.5	11.6 ± 7.9	11.0 ± 3.0	19.4 ± 9.0	13.9 ± 7.2
n	36	12	3	7	58
5-HIAA3	146.4 ± 75.0	106.9 ± 46.8	145.3 ± 94.8	184.6 ± 84.6*	142.5 ± 73.2
MMSE3	10.9 ± 6.7	3.6 ± 4.0	8.0 ± 6.1	18.3 ± 5.9	9.5 ± 7.1
n	17	8	3	5	33
For controls 5-HIAA	118.1 ± 34.9; $n = 13$				

176.9 ± 100.0 nmol/l). The paired-sample *t*-test used to study intrasubject changes between the three samples showed no significant differences in the 5-HIAA levels between the first and second or the second and third sample.

In delirious patients, the correlation between CSF 5-HIAA and the MMSE score was not statistically significant in the samples taken during the index admission ($r = -0.12$ and $r = 0.07$). The 5-HIAA: MMSE correlation was, however, significant in the 1-year sampling in the whole delirious patient population ($r = 0.43$; $P < 0.01$). Age had no correlation with 5-HIAA values either in the delirious patients ($r = 0.03$; $r = 0.17$, and $r = 0.06$, respectively) or in the controls. Out of the total 69 patients, 54 (77%) received neuroleptics at the beginning of the index admission, as did 23 out of the 44 patients after the 1-year follow-up period [52%]. The respective neuroleptic doses in chlorpromazine-equivalents were 143 ± 64, 133 ± 72, and 115 ± 87 mg. CSF 5-HIAA levels showed correlation with the neuroleptic dose in the first sample ($r = 0.34$; $P < 0.01$) but not in the subsequent samples ($r = 0.14$ and $r = -0.19$).

The annual death rates during the first, second, third and fourth follow-up years were 37%, 6%, 6%, and 17%, respectively. The time between the beginning of delirium and death was 583 ± 541 days and it did not differ among the various subgroups of delirious patients divided according to type of CNS disease. Proportional hazards model identified as association between the CSF 5-HIAA levels taken at the beginning of the index admission and with the life span after delirium ($z = 2.93$, $P = 0.007$). Patients who, after their delirium, needed prolonged institutional care in health-center wards or old-age nursing homes had lower 5-HIAA levels in the first sampling than rest of the patients (123.7 ± 54.7 versus 169.2 ± 56.9; $P = 0.01$).

Discussion

In this study, we found elevated CSF 5-HIAA levels during acute delirium in patients with vascular brain disease and also in patients with no apparent CNS disease. In patients with vascular brain disease, CSF 5-HIAA levels are increased in the CSF during the acute phase of brain infarction and decline to normal levels within the next weeks (Ferrarese et al. 1986). The elevated levels in our patients with vascular CNS disease probably reflect increased release from ischemic neurons. The finding of elevated 5-HIAA levels in patients with no apparent CNS disease in the first and third sampling is of interest and may reflect an increased turnover in these patients. In AD, the serotonergic neurons have been shown to be affected more severely than other monoamines. In our material, there was a trend that the lowest 5-HIAA levels were in AD patients. This is in line with the previous finding that decreased 5-HIAA/5-HT ratio in AD may indicate a decreased metabolic capacity of the affected serotonergic neurons (Reinikainen et al. 1988).

In a previous study of Banks and Vojnik (1978), raised CSF 5-HIAA levels have been observed during acute clozapine-induced or alcohol-withdrawal delirium. Their results indicated an increased release or turnover of serotonin, which in part may have been due to clozapine medication, although in some previous studies neuroleptic treatment has not been observed to alter the 5-HIAA levels significantly (e.g. Soininen et al. 1981). In the present study, there was a positive correlation between neuroleptic dose and CSF 5-HIAA in the first sample but not in the subsequent samples. The first positive correlation may be by chance or reflect the association between the extent of 5-HIAA release from damaged neurons and a need for symptomatic medication. None of our patients were on clozapine.

There is no convincing evidence of a relationship between changes in serotonergic neurons and the severity of dementia (Seeldrayers et al. 1985; Reinikainen et al. 1988). In our patients, correlations between CSF 5-HIAA and MMSE scores were not significant during the index admission, but reached a statistical significance at 1-year follow-up visit. The widespread disturbance of central neurotransmission may have obscured this correlation during and immediately after delirium. The results suggest, however, a paucity in the association between CSF 5-HIAA levels and cognition.

Previous studies have shown that low concentrations of CSF 5-HIAA are related to clinician- or self-reported aggression, behavioral difficulties, and irritability (Coccaro 1989). This involvement may be related to mood disturbances, such as depression, aggressive behavior, and anxiety, which are often encountered during and after acute delirium. Serotonergic projections from the reticular formation are also important in the maintenance of arousal and sleep-wake cycle, both of which are often severely disturbed in delirium (Lindesay et al. 1990).

The systemic diseases triggering delirium appear to alter brain function by interfering with metabolism in wide areas of the brain. In previous studies, the risk factors associated with delirium have in part been general markers for the severity of illness (Levkoff et al. 1992). The association observed in this study between the 5-HIAA levels during acute delirium and length of life after delirium suggests, however, that involvement of serotonergic neurons may have prognostic implications in delirium. The involvement of serotonergic neurons may also be responsible for the genesis of some symptoms of delirium, such as anxiety and depression, and also disturbance of arousal and sleep-wake cycle.

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