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An Association Between Low Levels of 5-HIAA and HVA in Cerebrospinal Fluid and Early Mortality in a Diagnostically Mixed Psychiatric Sample

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We followed up a sample of psychiatric patients (diagnoses predominantly schizophrenia and depression) who had participated in in-patient studies of their CSF over the past 15 years. The status of 73 former patients was confirmed, of whom 12 had died. Seven of these patients died at age ⩽40, largely of suicide, homicide, or accidental causes. These seven patients had significantly lower CSF 5-HIAA and HVA than living control patients. There were significant direct correlations between age at death and both CSF 5-HIAA and HVA in the deceased patients. The results offer support for CSF monoamine metabolites relating to early death in a diagnostically diverse sample of psychiatric patients.

Many studies (see Brown & Linnoila (1990) for a review) have demonstrated that low levels of 5-hydroxyindoleacetic acid (5-HIAA, the major serotonin metabolite) in cerebrospinal fluid (CSF) relate to a dimension of impulsive, suicidal, and aggressive behaviour. This relationship between 5-HIAA and impulsivity appears to cut across psychiatric diagnostic categories and normal controls. Low levels of CSF homovanillic acid (HVA, the major dopamine metabolite) have also been implicated in this dimension (e.g. Roy *et al*, 1989). HVA and 5-HIAA are usually correlated in human CSF, for reasons that are unclear (Jibson *et al*, 1990).

Psychiatric patients, such as those with schizophrenia, have higher rates of mortality than the general population (e.g. Allebeck & Wistedt, 1986; Anderson *et al*, 1991). To some degree this elevated mortality is due to increased suicide, but may relate as well to other causes that reflect a dimension of poor judgement, risk-taking, and impulsivity. Although impulsivity is a difficult construct to measure, mortality represents a reliable and objective dichotomisation. We performed a follow-up study of a sample of diagnostically mixed psychiatric patients who had previously taken part in CSF studies at our research centre. We hypothesised *a priori* that patients who died at an early age would have the lowest levels of CSF 5-HIAA and HVA. In addition, we hypothesised that among the deceased patients there would be a direct correlation between age at time of death and CSF metabolites (i.e. that early death is correlated with low serotonin and dopamine metabolite measures).

Method

The subjects were male in-patient veterans who had given written informed consent for CSF studies at the Stanford/VA Mental Health Clinical Research Center. Following further Institutional Review Board approval to perform the current analysis, we examined hospital records for the current status of all veteran patients who had consented for CSF studies from 1976 to 1990. Available records verified the status of 73 veterans, and we noted that 12 of the 73 patients had died since the time of research participation. The remaining 61 patients were active in out-patient or in-patient services. We were unable to verify the status of an additional 94 patients using hospital records, as these individuals had no recent or pending appointments and were not listed as deceased.

Seven of the 12 dead veterans had died at or below age 40. Records revealed that three of the seven patients died by suicide (two by gunshot, one by medication overdose). One of the young deceased patients was a homicide victim. Two patients died under seemingly accidental circumstances that make it difficult to attribute a single cause of death (i.e. one cannot rule out suicide in these cases): one of these patients died alone in a fire; the other drowned in a swimming pool. One patient died at age 37 of respiratory arrest. He had presented to the hospital with a gastrointestinal bleed following a period of heavy alcohol use; a pulmonary embolus was found at autopsy. This patient had a history of several serious suicide attempts. Five patients died at age 50 or older. Four of the five died of natural causes (two by myocardial infarction, one by carcinoma, one by sepsis secondary to pyelonephritis). A single patient in this older group died in a boating accident when a wave swept him overboard.

The young deceased (died ⩽age 40) patients met Research Diagnostic Criteria (RDC; Spitzer *et al*, 1978) for either schizophrenia or schizoaffective disorder ($n = 5$), major depression ($n = 1$), or depression superimposed on residual schizophrenia ($n = 1$). Diagnoses were typically obtained as

a result of consensus of a psychiatrist or psychologist who had conducted a clinical interview and an independent research assistant/nurse who had completed the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978). Five of the seven young deceased patients also met past or current RDC criteria for alcoholism and/or drug abuse disorders. The older deceased patients met RDC criteria for schizophrenia or schizoaffective disorder ($n=2$), hypomania ($n=1$), major depression ($n=1$), and depression superimposed on residual schizophrenia ($n=1$). Four of these five older deceased patients also met criteria for past or current alcoholism and/or drug abuse disorders.

We formed a comparison control group ($n=21$) for the seven young deceased patients by selecting for each one the three living patients whose lumbar punctures had been undertaken closest in time to that of the deceased patient. This strategy allows for a general matching in the time to potential follow-up for the deceased patients and their living controls, as well as controlling for any drifts in the CSF assays. The RDC diagnoses of the control group were schizophrenia or schizoaffective disorder ($n=13$), major depression ($n=6$), minor depression ($n=1$), and unspecified functional psychosis ($n=1$). Nine of these 21 patients also met criteria for past or present alcoholism and/or drug abuse disorders. We also formed a similar control group ($n=15$) for the five patients who died at age 50 or older. The diagnoses of these controls were schizophrenia or schizoaffective disorder ($n=10$), major depression ($n=4$), and minor depression ($n=1$). Five of these 15 control patients also met criteria for past or present alcoholism and/or drug abuse disorders.

CSF monoamine metabolite data were available from previous in-patient research participation. All patients had been free of psychiatric treatment medication (except chloral hydrate) for two or more weeks at the time of the lumbar puncture. Patients typically fasted and remained in bed overnight before the lumbar puncture. In almost all cases the lumbar puncture was performed in the lateral decubitus position at approximately 8.00 a.m. CSF monoamine concentrations were determined by gas chromatography/mass spectrometry (Faull *et al*, 1979). Non-parametric analyses were employed as conservative tests in the relatively small samples.

Results

We initially questioned whether CSF values for the documented living patients differed from those for patients who were lost to follow-up. We noted that in the group lost to follow-up the CSF 5-HIAA levels (mean 22.19 (s.d. 10.3) ng/ml) and HVA levels (mean 33.99 (s.d. 15.3) ng/ml) were similar to the values for the living controls that were matched to the deceased patients (see Table 1). Accordingly, no sampling bias appears likely in the identification of our living controls.

Table 1 displays data for the deceased groups and living control groups. CSF 5-HIAA concentrations for the young deceased were significantly lower ($P<0.01$, one-tailed, Mann–Whitney U test) than for their control group of 21 living patients. HVA concentrations were also significantly lower ($P<0.05$, one-tailed, Mann–Whitney U test) in the young deceased than in their living controls. No significant differences in either CSF metabolite were observed between older deceased patients and their controls. Although the young deceased patients tended to be somewhat younger at the time of lumbar puncture than their controls (deceased 34.42 (s.d. 2.6) years, controls 40.81 (s.d. 11.5) years), this difference was not statistically significant. We found no significant correlations (Spearman) between age at time of lumbar puncture and CSF metabolites in any of the control groups. Accordingly, our between-group differences are not likely to be due to an age-related effect on CSF metabolite concentrations.

A further analysis evaluated Spearman correlations between age at time of death and CSF measures in the full sample of 12 deceased patients. Statistically significant correlations were obtained between age at death and both CSF 5-HIAA ($r_S=0.575$, $P<0.05$, one-tailed) and HVA ($r_S=0.599$, $P<0.05$, one-tailed). In other words, lower levels of both monoamine metabolites were associated with shorter life-span in the deceased sample. It was also found that CSF 5-HIAA and HVA were correlated both in the total sample of deceased patients ($n=12$, $r_S=0.839$, $P<0.01$) and in the total sample of living patients ($n=36$, $r_S=0.432$, $P<0.05$).

We performed additional analyses to determine if extraneous variables could have accidentally contributed to our findings. CSF metabolites can have a gradient (Banki & Molnar, 1981) and so body height could have influenced the measures. However, we noted that the height distribution of the young deceased patients (mean 177.6 (s.d. 8.1) cm) was almost identical to that of their comparison living controls (mean 178.1 (s.d. 9.3) cm). In addition, one could hypothesise that alcohol/drug abuse could relate to monoamine metabolite differences. Accordingly, considering patients from the primary analysis sample (12 deceased subjects and 36 living controls) we compared those who

Table 1
CSF 5-HIAA and HVA concentrations among young and older deceased patients and their paired living control patients

	CSF 5-HIAA levels: ng/ml			CSF HVA levels: ng/ml		
	Mean	s.d.	Range	Mean	s.d.	Range
Seven patients who died at age $\leqslant 40$	11.79	3.64	5.4–15.4	22.77	10.18	10.3–38.1
Five patients who died at age $\geqslant 50$	24.32	10.78	6.0–32.0	40.84	18.82	14.2–61.8
Twenty-one living control patients paired with the seven patients who died at age $\leqslant 40$	24.94	11.47	7.8–59.4	33.48	15.60	7.3–69.4
Fifteen living control patients paired with the five patients who died at age $\geqslant 50$	22.32	7.39	14.5–37.10	35.80	11.79	14.2–59.1

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were positive for past or present RDC alcoholism and/or drug abuse disorders ($n = 23$) with those who were negative ($n = 25$). There were no differences in the CSF monoamine metabolite levels based on this grouping (positive ETOH/drug patients – mean 5-HIAA 22.1 (s.d. 12.3) ng/ml, mean HVA 31.8 (s.d. 14.9) ng/ml; negative ETOH/drug patients – mean 5-HIAA 22.2 (s.d. 8.1) ng/ml, mean HVA 34.9 (s.d. 14.5) ng/ml. It should be noted that our study pooled patients with mixed diagnoses. However, previous work by our group (Berger *et al*, 1980) and others (see Meltzer & Lowy (1987) and Losonczy *et al* (1987) for reviews) has failed to find differences in CSF monoamine metabolites between diagnostic groups.

Discussion

Using a sample of patients studied at our research centre over the past 15 years, we noted evidence for a relationship between early death and low CSF values of both 5-HIAA and HVA. Patients who died at age 40 or younger (typically of suicide, homicide, or accidental causes) had significantly lower CSF metabolite levels than living controls. In fact, the highest 5-HIAA level in the young deceased patients was approximately a standard deviation below the mean for their control group. Additionally, among the full sample of deceased patients of all ages, there was a statistically significant direct correlation between age at time of death and both CSF 5-HIAA and HVA. Because there was no correlation between age at time of lumbar puncture and the CSF metabolites in the larger groups of living patients, it is unlikely that the relationship in the deceased patients was due to a simple age effect on the CSF measures. As in previous studies (e.g. Jibson *et al*, 1990), CSF measures of 5-HIAA and HVA were significantly correlated; accordingly, the degree to which mortality is linked to a single monoamine system remains unclear.

Several biochemical and psychological factors may modulate impulsive, aggressive, or risk-taking behaviour. Our study suggests that young male psychiatric patients with low CSF 5-HIAA and HVA values are at a relatively high risk for violence-associated or accidental death. We further hypothesise that the risk for suicide and accidental death is decreased in those patients who survive past the age of 40. The question of whether there is, in fact, some protective effect of increased age, as from decreased circulating testosterone, deserves further study.

While our data provide support for an association of low CSF 5-HIAA and HVA with early mortality and with violence-associated and accidental death, we recognise that given our relatively small samples we could have under-represented violent deaths in the older deceased group. In general, however, our findings relating to early death in a diagnostically mixed psychiatric sample add further support to a growing literature implicating CSF 5-HIAA and HVA in a broad behavioural dimension of impulsivity.

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