ORIGINAL ARTICLE

Early-Onset Alcoholics Have Lower Cerebrospinal Fluid 5-Hydroxyindoleacetic Acid Levels Than Late-Onset Alcoholics

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Background: We investigated the interrelationships of age at onset of excessive alcohol consumption, family history of alcoholism, psychiatric comorbidity, and cerebrospinal fluid monoamine metabolite concentrations in abstinent, treatment-seeking alcoholics.

Methods: We studied 131 recently abstinent alcoholics. Supervised abstinence was maintained on a research ward at the National Institutes of Health Clinical Center for a minimum of 3 weeks. All alcoholics received a low-monoamine diet for a minimum of 3 days before lumbar puncture. Lumbar punctures were performed in the morning after an overnight fast. Monoamine metabolites and tryptophan in cerebrospinal fluid were quantified with liquid chromatography by means of electrochemical detection. Psychiatric diagnoses were established from blind-rated Schedule for Affective Disorders and Schizophrenia–Lifetime version interviews administered by a research social worker. Severity and age at onset of excessive alcohol consumption were documented with a structured lifetime drinking history questionnaire and with selected alcoholism screening questionnaires (CAGE and Michigan Alcoholism Screening Test). Family history of alcoholism was obtained from the probands.

Results: A majority of the treatment-seeking, primarily white male alcoholics had a lifetime history of psychiatric disorders other than alcoholism. None fulfilled criteria for antisocial personality disorder. Early-onset alcoholics (onset of excessive consumption before 25 years of age) had a more severe course of alcoholism and lower mean cerebrospinal fluid 5-hydroxyindoleacetic acid concentration than late-onset alcoholics. Patients who reported both parents to be alcoholics had particularly low mean cerebrospinal fluid 5-hydroxyindoleacetic acid, homovanillic acid, and tryptophan concentrations.

Conclusion: Among treatment-seeking alcoholics, early age at onset is generally associated with a more severe course of alcoholism and lower cerebrospinal fluid 5-hydroxyindoleacetic acid concentration.

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EPIDEMIOLOGIC surveys have found that alcoholism is the most common mental or substance abuse disorder among men in the United States.[1] Like most mental disorders, alcoholism is heterogeneous and tends to occur in families. To facilitate psychobiologic and molecular genetic studies on alcoholism, criteria have been proposed to define relatively homogeneous subgroups.

Cloninger et al[2] developed a classification scheme for alcoholism, based on a large-scale adoption study conducted in Stockholm, Sweden, that has had great heuristic value. Two subtypes of alcoholism were defined, types 1 and 2. Seventy-five percent of men and all women in the Stockholm sample fulfilled criteria for type 1 alcoholism. These patients were characterized by a relatively late age at onset of heavy drinking, anxious personality traits, and adverse environmental conditions during development. The type 2 alcoholics were all men, had alcoholic fathers with antisocial traits, began heavy drinking at an early age, exhibited antisocial personality traits, and a functional adoptive family did not reduce the risk of expression of the inherited vulnerability.[2] Irwin et al[3] and Lamparski et al[4] were only partially successful in validating the findings of Cloninger et al.[2] Irwin et al[3] found that, regardless of family history, the main factor defining the course and characteristics of an alcoholic seeking treatment was the age at onset. Lamparski et

See Patients and Methods on next page

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PATIENTS AND METHODS

PATIENTS

All participants (n=131) were selected from recently abstinent alcoholics undergoing research and treatment on the inpatient research ward of the National Institute on Alcohol Abuse and Alcoholism at the National Institutes of Health Clinical Center in Bethesda, Md. Most participants resided in the Washington, DC, metropolitan area and became aware of the program by physician referral, word of mouth, or weekly advertisements in a major metropolitan newspaper. All patients met Research Diagnostic Criteria[11] for alcoholism and had negative results of urine drug screens at the time of admission. Written informed consent was obtained before the start of the study.

PROCEDURES

The standard procedure for obtaining CSF samples consisted of at least 3 weeks of supervised abstinence from alcohol on a locked research ward and a minimum of 3 days on a low-monoamine diet.[12] The low-monoamine diet excluded certain beverages (eg, chocolate drinks), fruits (eg, bananas), nuts (eg, walnuts), vegetables (eg, tomatoes), meats (eg, chicken livers), dairy products (eg, aged cheese), fish (eg, smoked fish), and soft drinks sweetened with aspartame. Lumbar punctures were performed between 9 and 10 AM, after overnight bed rest and fast. Approximately 32 mL of CSF was collected while the patient was in the left lateral decubitus position. The first 12 mL of CSF was collected as a single aliquot into a tube on wet ice, mixed thoroughly, aliquoted to 1-mL test tubes, and stored immediately at −70°C. None of the samples was ever thawed before analysis.

Concentrations of the major CSF metabolites of norepinephrine (3-methoxy-4-hydroxyphenylglycol [MHPG]), dopamine (homovanillic acid [HVA]), serotonin (5-HIAA), and the serotonin precursor tryptophan were determined with high-pressure liquid chromatography by means of a slight modification of the method of Scheinin et al.[13] Analyses were conducted in a single run. The within-run coefficient of variation for all of the analytes was less than 10%.

All alcoholics were administered a structured psychiatric instrument, the Schedule for Affective Disorders and Schizophrenia–Lifetime version,[14] by a social worker. The resulting diagnoses were based on a subsequent blind rating by another social worker and a psychiatrist. Diagnoses were reviewed and any inconsistencies were resolved by a senior psychiatrist (G.L.B.). Diagnoses were categorized as current, past, and lifetime (current and/or past). Alcoholism screening instruments (ie, the Michigan Alcoholism Screening Test[15] and the CAGE[16]) were administered, and information on recent and chronic alcohol consumption and alcohol-related behavior was obtained from structured research questionnaires completed by the patients.[17] Information on current and past use of other drugs, including cigarettes and caffeine, and parental history of alcoholism was collected from the patients, and selected laboratory variables (aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltransferase) were quantified.

All statistics were computed by means of the BMDP statistical software package.[18]

al[4] reported difficulty in applying the Cloninger classification scheme because a majority of alcoholics could not be confidently assigned to either type.

von Knorring et al[5] operationalized a two-group classification scheme based primarily on age at onset and secondarily on complications thought to be consequences of antisocial behavioral traits. This scheme results in every alcoholic being assigned to one of the subgroups. Similar to the Cloninger et al[2] criteria, von Knorring et al[5] called late-onset alcoholics type 1 and early-onset type 2. Unlike Cloninger et al,[2] von Knorring et al[5] did not require a paternal family history of alcoholism for type 2. The classification scheme of von Knorring et al[5] has proved useful in psychobiologic studies. Type 2 alcoholics have lower mean platelet monoamine oxidase activity than type 1 alcoholics and healthy volunteers[6]; this biochemical trait has been associated with the personality trait of sensation seeking. Approximately half of type 2 alcoholics have also been reported to experience a strong urge to consume alcohol in response to an intravenous infusion of the serotonin 2C receptor agonist meta-chlorophenylpiperazine.[7] Studies of early-onset, violent Finnish alcoholics have demonstrated that their impaired impulse control is associated with a low mean concentration of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin, in the cerebrospinal fluid (CSF).[8,9]

Based on the above findings, we postulated that alcoholics who engage in excessive alcohol consumption by 25 years of age (type 2) have reduced central serotonin turnover.[10] In the present study, we tested this hypothesis as well as determined the effects of (1) family history of alcoholism, (2) degree of antisocial behavioral traits, and (3) depression concurrent with alcoholism on CSF 5-HIAA concentrations in a large group of carefully characterized alcoholics after a minimum of 3 weeks of supervised abstinence. Levels of CSF monoamine metabolites were determined after at least 3 days on a low-monoamine diet and were quantified in a single large assay to exclude interassay variability.

RESULTS

The average (±SD) age of the alcoholics was 39.2±9.8 years. The sample was composed of 122 men and nine women, consisting of 112 whites, 17 African Americans, and two Hispanics.

The age at onset of excessive alcohol consumption was calculated by subtracting the years of excessive consumption (more than three drinks per 24 hours, on the average) from the current age. The 90 alcoholics who had an onset of excessive consumption by 25 years of age had lower levels of 5-HIAA than the alcoholics with an onset after 25 years of age (P=.01; **Figure 1**). There were

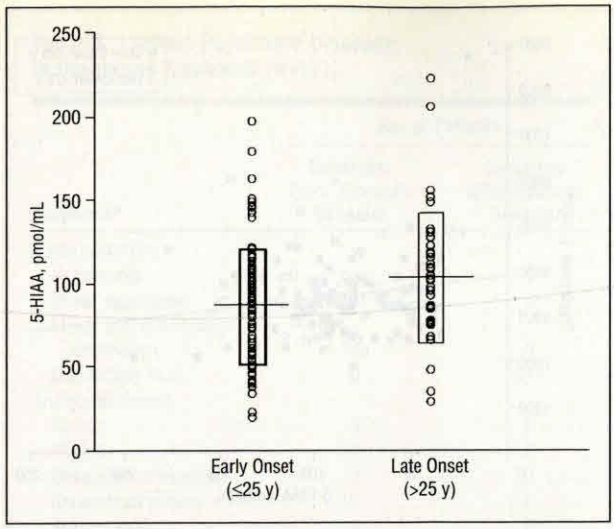

Figure 1. *Mean±SD cerebrospinal fluid levels of 5-hydroxyindoleacetic acid (5-HIAA) in alcoholics as a function of age at onset of excessive alcohol consumption (P=.01).*

no differences in CSF HVA, MHPG, or tryptophan concentrations between the groups (**Table 1**).

Early-onset alcoholics were younger (36.3±8.8 years) than late-onset alcoholics (46.1±8.7 years) ($P<.001$). They consumed more alcohol per drinking occasion during the preceding 6 months, had more years of excessive alcohol consumption, and had higher CAGE and Michigan Alcoholism Screening Test scores (**Table 2**). There were no group differences in frequency of drinking during the past 6 months or in time between the last drink and the lumbar puncture.

There were no differences in CSF 5-HIAA, HVA, MHPG, or tryptophan levels between alcoholics with only paternal alcoholism, only maternal alcoholism, or either parent exhibiting alcoholic behavior and the rest of the sample. The 12 alcoholics with paternal *and* maternal alcoholism had significantly lower levels of 5-HIAA (79±5 vs 92±38 pmol/mL; $P=.03$), HVA (132±30 vs 156±63 pmol/mL; $P=.03$), and tryptophan (2976±655 vs 3536±912 pmol/mL; $P=.04$) than the rest of the sample.

Relationships among various predictor variables and CSF 5-HIAA, HVA, MHPG, and tryptophan concentrations were determined by means of multiple regression techniques wherein each dependent variable, one at a time, was predicted by those independent variables with which it was significantly correlated ($r\geq.17$; $P\leq.05$). Fifty-five percent of the variance in 5-HIAA level was explained by levels of HVA, tryptophan, and MHPG and the CAGE score ($P<.001$). Higher levels of HVA predicted higher levels of 5-HIAA ($P<.001$), and lower levels of tryptophan tended to predict higher levels of 5-HIAA ($P=.06$). Neither MHPG level ($P=.40$) nor the CAGE score ($P=.81$) was significant when the other variables were considered.

Fifty-six percent of the variance in HVA level was explained by levels of 5-HIAA and MHPG, years of excessive alcohol consumption, and CAGE score ($P<.001$). Increasing levels of 5-HIAA and MHPG predicted higher levels of HVA ($P<.001$ and $P=.03$, respectively), and increasing years of excessive alcohol consumption tended to predict lower levels of HVA ($P=.08$). The CAGE did not explain significant amounts of variance ($P=.78$) when the other variables were considered.

Table 1. Concentrations of CSF Variables*

	Mean±SD		
	Early Onset (n=90)	Late Onset (n=41)	*P*
5-HIAA, pmol/mL	85.6±34.7	103.6±38.9	.01
HVA, pmol/mL	149.5±62.3	163.4±58.5	.24
MHPG, pmol/mL	43.4±12.1	43.4±13.4	.99
Tryptophan, pmol/mL	3515±989	3437±692	.65

**CSF indicates cerebrospinal fluid; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; and MHPG, 3-methoxy-4-hydroxyphenylglycol.*

Fourteen percent of the variance in MHPG level was explained by age and levels of HVA and 5-HIAA ($P<.001$). Increasing age predicted higher MHPG levels ($P=.01$), and increasing HVA levels predicted higher MHPG levels ($P=.02$). The level of 5-HIAA did not explain significant amounts of variance ($P=.87$) when the other variables were considered.

Seventeen percent of the variance in tryptophan was explained by levels of 5-HIAA, aspartate aminotransferase (45±47 U/L), γ-glutamyltransferase (127±188 U/L), and alanine aminotransferase (52±62 U/L) ($P<.001$). Decreasing levels of 5-HIAA predicted higher levels of tryptophan ($P=.004$; **Figure 2**), and increasing levels of aspartate aminotransferase predicted higher levels of tryptophan ($P=.04$); there was a trend for higher levels of γ-glutamyltransferase to predict higher levels of tryptophan ($P=.08$). Levels of alanine aminotransferase did not predict ($P=.26$) tryptophan levels when the other variables were considered.

In addition to satisfying Research Diagnostic Criteria for a lifetime (current and/or past) diagnosis of alcoholism, 90 alcoholics (69%) also satisfied criteria for other lifetime psychiatric disorders. Thirty-six alcoholics (27%) had diagnoses that coexisted with alcoholic behavior, while 54 (41%) had psychiatric disorders that were separable from alcoholic behavior, ie, current diagnosis of alcoholism and past psychiatric diagnosis or past diagnosis of alcoholism and current psychiatric diagnosis.

In the 54 alcoholics who satisfied criteria for other lifetime psychiatric disorder(s) that were separable from alcoholic behavior, most frequent were drug use, mood, and anxiety disorders (**Table 3**). Thirty-one had one other diagnosis, 13 had two, five had three, and five had four or more diagnoses.

Sixty-eight alcoholics (52%) had other lifetime psychiatric disorders that were *not* separable from alcoholic behavior, with the most frequent being mood and anxiety disorders (Table 3). Of these 68, 32 (47%) had some psychiatric disorders that were distinct from alcoholic behavior and some that were not separable.

Alcoholics with a lifetime diagnosis of some form of depression (major, minor or intermittent, or depres-

Table 2. Alcoholism-Related Variables*

	Mean±SD		
	Early Onset (n=90)	Late Onset (n=41)	*P*
CAGE (4 items)	3.8±0.5	3.5±0.8	.02
MAST (25 weighted items)	43.8±22.3	35.2±6.9	.02
Days between last drink and lumbar puncture	38.0±22.1	34.8±22.4	.44
No. of drinking occasions in last 6 mo	126.9±55.2	127.6±53.9	.94
Alcohol consumed per occasion in last 6 mo, g†	221.4±115.4	170.6±154.8	.04
Years of excessive alcohol consumption (yearly average, >3 drinks/d)	18.2±9.0	9.7±7.8	<.001

**CAGE is an alcoholism screening questionnaire that contains four structured research questions. MAST indicates Michigan Alcoholism Screening Test.*

†A standard drink contains 11.2 to 14.0 g of alcohol, depending on beverage.

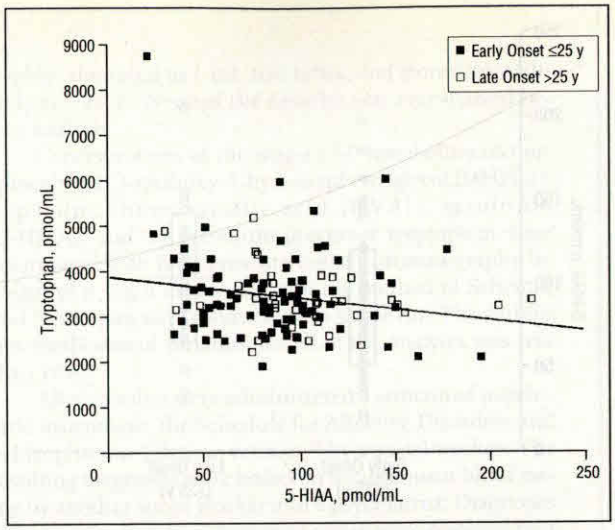

Figure 2. *Relationship between 5-hydroxyindoleacetic acid (5-HIAA) and tryptophan (r=−.19; P=.03).*

sion not otherwise specified) did not have low CSF 5-HIAA levels. Moreover, there were no differences in 5-HIAA levels between alcoholics with no diagnosis of depression and those with major depression; major depression or depression not otherwise specified; minor or intermittent depression; or minor, intermittent, or depression not otherwise specified.

Nineteen alcoholics reported attempting suicide, and they did not differ from the others in 5-HIAA, HVA, MHPG, or tryptophan levels. Early- and late-onset (n=14 and 5, respectively) alcoholics were equally likely to have attempted suicide (15.6% and 15.2%, respectively). Moreover, there were no differences in the seriousness of intent scores according to the Schedule for Affective Disorders and Schizophrenia–Lifetime version for the most serious attempt.

Comparisons among prevalence of psychiatric diagnoses in early- and late-onset alcoholics showed that individuals with early onset were also more likely to have a lifetime diagnosis of drug use disorder ($P<.03$).

Although no alcoholics satisfied Schedule for Affective Disorders and Schizophrenia–Lifetime version criteria for antisocial personality disorder, summed scores across the four criteria disclosed higher values for early- than for late-onset alcoholics ($P=.001$). The early-onset alcoholics exhibited poorer occupational performance ($P<.001$) and more childhood ($P=.001$) and adult ($P=.001$) behaviors defined as antisocial than the late-onset alcoholics. Occupational, childhood, adult, and summed antisocial behavior scores were not significantly correlated with 5-HIAA levels for early- or late-onset alcoholics or for the entire sample. Also, there was no relationship between a father's alcoholic status and degree of antisocial traits in the alcoholic offspring.

COMMENT

The present study was designed to determine relationships among levels of various CSF monoamine metabolites, alcohol-related behavior, psychiatric comorbidity, and parental alcoholism. Quantification of alcohol-related behavior and determination of parental alcoholism was based on self-report. Psychiatric comorbidity was determined by administration of the Schedule for Affective Disorders and Schizophrenia–Lifetime version, with subsequent blind rating of responses by clinicians who used Research Diagnostic Criteria. The levels of CSF monoamine metabolites were determined in a single large assay after at least 3 days of low-monoamine diet and 3 weeks of supervised abstinence.

Alcoholics who began excessive alcohol consumption by 25 years of age (early onset) had significantly lower CSF 5-HIAA concentrations than alcoholics with a late onset (Figure 1). The HVA, MHPG, and tryptophan concentrations were similar among the early- and late-onset alcoholics (Table 1). Even though early-onset alcoholics had a more extensive alcohol history than late-onset alcoholics (Table 2), alcohol-related behaviors or alcohol consumption did not correlate with CSF 5-HIAA concentrations in either the total sample or the two subsamples.

In addition to exhibiting more severe alcoholism, early-onset alcoholics also exhibited more antisocial behavioral traits. Similar findings have been reported by Irwin et al.[3] Neither study, however, included patients who met criteria for antisocial personality disorder. These findings differ from those of Cloninger,[19] who suggested that late-onset alcoholics exhibit a more severe alcoholism and have a poorer prognosis.

An earlier study from our program[20] also reported lower CSF 5-HIAA concentrations in early- vs late-onset alcoholics. This finding did not, however, achieve statistical significance. The major differences between the two studies are the larger sample size and the elimination of between-assay variability in the present study and a different age at onset criterion. The present age at onset criterion was selected to test directly the hypotheses of Cloninger et al[2] and Irwin et al.[3] Although other investigators have reported reduced CSF 5-HIAA concentrations in abstinent alcoholics, they have not addressed

Table 3. Lifetime Psychiatric Disorders in Diagnosed Alcoholics (N=131)

Diagnosis*	No. of Patients: Separable From Alcoholic Behavior	No. of Patients: Coexistent With Alcoholic Behavior
Mood disorders		
Hypomania	1	0
Major depression	7	0
Minor and intermittent depression	14	0
Depression NOS	0	61
Anxiety disorders		
Panic	6	0
Phobia	4	0
Obsessive compulsive	2	0
Generalized anxiety	10	0
Anxiety NOS	9	0
Posttraumatic stress	2	0
Drug use disorder	29	1
Psychotic disorders NOS	0	3
Organic disorder NOS	0	2
Attention deficit disorder	0	2

**More than one diagnosis per individual is possible. NOS indicates not otherwise specified.*

the issue of subgrouping. Ballenger et al[21] studied abstinent, young male alcoholics and reported one of the largest differences between alcoholics and controls. The demographics of their sample suggest that a large proportion of the patients were early-onset alcoholics. Banki[22] reported low CSF 5-HIAA levels in recently abstinent alcoholic men and women, and Takahashi et al[23] found low CSF 5-HIAA concentrations in alcoholics who had undergone severe withdrawal.

Parental alcoholism had little effect on levels of monoamine metabolites, except that lower concentrations of 5-HIAA, HVA, and tryptophan were observed in the 12 alcoholics who reported that both of their parents were alcoholic. Determination of family history of alcoholism by structured questioning of the alcoholics rather than having additional verification by relatives or significant others is a less-than-optimal practice,[24] even though it yields more accurate results for the family history of alcoholism than for most other mental disorders.[25]

The observed interrelationships among CSF monoamine metabolite concentrations are generally compatible with the existing literature.[26] Higher levels of HVA and lower levels of tryptophan predicted higher levels of 5-HIAA. Higher levels of 5-HIAA and MHPG predicted higher levels of HVA, whereas increasing years of excessive alcohol consumption tended to predict lower levels of HVA. Increasing age and HVA levels predicted higher levels of MHPG, as previously reported.[27] Decreasing levels of 5-HIAA and increasing levels of aspartate and alanine aminotransferase predicted higher levels of tryptophan. The negative relationship between CSF tryptophan and 5-HIAA concentration (Figure 2) is seemingly contrary to the suggestion that free tryptophan crossing the blood-brain barrier drives the rate of serotonin synthesis.[28] Virkkunen and Narvanen[29] found, however, that Finnish violent alcoholics with low CSF 5-HIAA concentrations had high ratios of plasma tryptophan to large neutral amino acids. These data are in accordance with a recent suggestion that in humans, under certain circumstances, the activity of tryptophan hydroxylase per se, rather than the free extracellular tryptophan concentration, may be rate limiting for central serotonin turnover.[30]

In addition to satisfying Research Diagnostic Criteria for a lifetime diagnosis of alcoholism, 90 individuals also satisfied criteria for other lifetime psychiatric disorders. This relatively high prevalence of comorbidity has been reported by others[31,32] and consisted of disorders that were separable from alcoholic behavior as well as those that were not separable. In the 54 alcoholics with past or present psychiatric disorders that were separable from alcoholic behavior, the most frequent were drug use, mood, and anxiety disorders (Table 3). Mood and anxiety disorders were the most frequent psychiatric disorders observed (Table 3) in the 68 alcoholics for whom the psychiatric disorders were not separable from alcohol-related behavior.

In studies on violent, antisocial alcoholics in Finland, the patients with a family history of paternal alcoholism had the lowest CSF 5-HIAA concentration.[33] The Finnish patients, as a group, had much lower CSF 5-HIAA concentrations than the present sample. Because CSF 5-HIAA is influenced by genetic and environmental variables, it may be that the genetic variation is more apparent at the extremes of the distribution, such as was observed among the Finnish patients. A history of suicide attempts was also related to extremely low CSF 5-HIAA levels among alcoholic violent Finns,[8,34] but the present study replicates our previous finding[35] of a lack of a relationship between CSF 5-HIAA and suicide attempts among American treatment-seeking alcoholics, free of personality disorders and with 5-HIAA levels in the normal range.

Rosenthal et al[36] reported that depressed patients, who themselves did not have a drinking problem but had a family history of alcoholism, had a lower mean CSF 5-HIAA concentration than equally depressed patients free of a family history of alcoholism. Although family history of depression was not determined in the present study, a personal history of depressive episodes was not associated with a low CSF 5-HIAA concentration.

In conclusion, we found that early-onset alcoholics had a lower mean CSF 5-HIAA concentration than late-onset alcoholics. Early-onset alcoholics also had a more severe course of illness than late-onset alcoholics. Psychiatric comorbidity and family history positive for paternal alcoholism did not correlate with CSF 5-HIAA, but a history of alcoholism in both parents was correlated with low CSF 5-HIAA concentration.

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