Familial Transmission of Depression and Alcoholism

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• The familial transmission of major depression and alcoholism among probands who had depression and alcoholism was examined. Our findings indicated that depressives without alcoholism did not transmit alcoholism, and probands with depression and alcoholism tended to transmit both depression and alcoholism. This confirms the observation that depression and alcoholism are not manifestations of the same underlying disorder. An increased risk of anxiety disorders in the relatives of probands with alcoholism, which could specifically be attributed to the presence of alcoholism in addition to an anxiety disorder in the proband, was also observed. This suggested that the alcoholism in these probands may result from self-medication of anxiety symptoms. The results of this study underscore the importance of examining combinations of diagnoses in patients in decreasing the heterogeneity of diagnostic categories.

(*Arch Gen Psychiatry* 1985;42:367-372)

Although an association between affective disorder and alcoholism has been frequently reported, the nature of this association is unclear.[1-4] This is partly because the heterogeneity of both disorders has made it difficult to determine the relative contribution of genetic and environmental components to either disorder alone. The manifestation of both disorders in individuals and/or families has rendered the analysis of their association even more complex. Family studies have enabled investigators to examine this relationship by providing data regarding patterns of transmission within families.

The combination of alcoholism and major depression within individuals has been frequently observed in both treated and untreated populations. Cadoret and Winokur[5] reported that 39% of the alcoholic patients in their study also had primary or secondary major depression. In a community survey, Weissman and Myers[6] found that 68% of those subjects with alcoholism met Research Diagnostic Criteria (RDC) for a lifetime diagnosis of either major or minor depressive disorder. However, there are few clinical differences between alcoholics with either primary or secondary depression.[5] Indeed, Woodruff et al[4] reported that patients with alcoholism and depression resemble alcoholic patients without depression more than they resemble patients with depression only.

Family studies of alcoholic probands have yielded consistently higher rates of both alcoholism and depression than would be expected in the general population.[2,3,7,8] The family studies of depressed probands, however, have been less conclusive. Although Winokur[3] found an excess of alcoholism in the relatives of probands with early onset depression, Gershon et al[8] and Weissman et al[9] found no increase in alcoholism among the relatives of depressed probands in comparison with normal probands. The relationship becomes even less clear when the disorders are broken down according to the sex of the proband or the primary-secondary distinction based on the order of onset of disorders.[10] In general, secondary alcoholics with primary depression have significantly fewer alcoholic relatives and more depressed relatives than do primary alcoholics.[2,3,7] Despite the clustering of depression and alcoholism within individuals and in families, Cloninger et al[7] have demonstrated that the etiology of the two disorders is heterogeneous and concluded that they are not manifestations of the same underlying illness. Similarly, Angst[11] concluded that depression and alcoholism are independent disorders, and that alcoholism is not a masked form of depression.

In our case-control family study of first-degree relatives of normal and depressed probands, we found that the relatives of probands with primary nonbipolar affective disorder had significantly greater rates of alcoholism (14.4%) than relatives of normal probands (9.0%). However, relatives of severely depressed (hospitalized) probands did not have significantly higher rates of either alcoholism or

Accepted for publication May 17, 1984.

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Table 1.—Number of Probands and Relatives by Presence of Alcoholism in Probands

Proband Group	No. of Probands	No. of Relatives
Normal	82	521
Depression, no alcoholism	114	692
Depression + alcoholism	19	118
Total	**215**	**1,331**

depression than the relatives of mildly depressed (nonhospitalized) probands.[12] Because our severity dimension among probands was not validated by rates of illness among relatives, we have restratified the depressed probands in numerous ways.[13,14] This report will focus on the risk of depression and alcoholism in relatives of depressed probands with alcoholism.

PATIENTS AND METHODS

Probands

There were a total of 215 probands: 89 with mild (nonhospitalized) major depression, 44 with severe (hospitalized) major depression, and 82 normal community controls. The control group was drawn from a population sample and had no evidence of psychiatric disorder or treatment either by history or at three interviews obtained between 1967 and 1976. The three proband groups were group matched by sex and age.

Restratification of Probands

For this report, the depressed probands were reclassified according to the presence or absence of alcoholism. The onset of depression in all of the probands preceded the onset of alcoholism. Estimates of the age of onset of each disorder were made by a psychiatrist using all available information including a modified Schedule for Affective Disorders and Schizophrenia (SADS-L) interview,[15] information obtained from numerous family members, and medical records from any episode of illness for which the proband had received treatment. If there was evidence that the proband met the RDC[16] for alcoholism prior to the first episode of depression, the proband was excluded from the study. Similarly, probands with antisocial personality or primary drug abuse were excluded. The number of probands and relatives in the new proband groups are presented in Table 1.

Diagnoses in Relatives

Lifetime diagnostic estimates using modified RDC[16] were made on a total of 1,331 living and deceased first-degree relatives of the probands using a best-estimate procedure.[17] The sources of information that we used in making diagnoses included direct interviews (30%), medical records, and family history information that was obtained systematically from multiple informants. Because the adequacy of information regarding the relatives varied, diagnoses were made according to the degree of certainty of the diagnosis (ie, possible, probable, or definite). All diagnoses were made blindly with respect to the status of the proband. A more detailed description of the design and methods of this study has been presented by Weissman et al.[12]

The diagnoses in relatives were not mutually exclusive. Thus, if an individual met the criteria for two disorders, both diagnoses were made regardless of the order of manifestation of the disorders. In the present analysis, the following disorders were examined: major depression, which differed from the RDC in requiring a four-week duration and evidence of social role impairment; anxiety disorder, which included obsessive-compulsive disorder, agoraphobia, simple and social phobia, panic disorder, and general anxiety disorder, all of which were specified by modified *DSM-III* symptomatic criteria with evidence of social role impairment; alcoholism, which included possible, probable, or definite RDC-defined alcoholism; and antisocial personality, which was also defined according to RDC.[16] The reliability of the family history method for ascertaining psychiatric history in this study has been described by Thompson et al.[18] The diagnosis of alcoholism was one of the most reliable of the diagnostic categories.[17,18]

Table 2.—Sociodemographic and Clinical Characteristics of Probands

	Proband Group		
	Normal (N=82)	Depression, No Alcoholism (N=114)	Depression + Alcoholism (N=19)
Sex, %*			
M	41	36	47
F	59	64	53
Index of social position, %†			
I, II, III	42	54	42
IV, V	58	46	58
Religion, %†			
Catholic	73	58	53
Protestant	19	21	26
Jewish	7	7	5
Other/none	1	14	16
Marital status, %‡			
Single	5	11	21
Married	83	65	53
Separated, divorced, widowed	12	24	26
Mean age, yr†	49	46	42
Mean age of onset, yr			
Major depression*	. . .	33	28
Alcoholism*	. . .	. . .	35

*P was not significant.
†$P = .05$.
‡$P = .01$.

Statistical Analysis

The proportional hazards (PH) model, a general quasi-parametric multivariate model introduced by Cox, was used to analyze the data.[19,20] The PH model applies the multiple-regression method to a survival distribution, or another one-time event such as onset of a disorder. The PH procedure yields a ratio of the hazards, or the age-specific incidence, of the outcome variables (ie, diagnosis of relatives) for the groups of interest, while simultaneously controlling for other independent variables that may be related to the outcome. A stepwise model with all main effects and two-way interactions was used to fit the data.

In the present analysis, the ratios of the age-specific incidence of major depression, anxiety disorder, and alcoholism among relatives of depressed probands with and without alcoholism were examined. From an earlier analysis of these data using the original proband groups (normal, mild, and severe), the rate of major depression among first-degree relatives was found to vary according to the sex and year of birth of the relative and the interview status.[12] Therefore, the effects of the year of birth of the relative, the sex of the proband, the sex of the relative, and the interview status were included in each model. Statistical significance of the effects was determined by the χ^2 statistic using maximum likelihood estimates. The computer program used in the analysis was the Proportional Hazards General Linear Models procedure of the Statistical Analysis System.[21]

RESULTS

Sociodemographic and Clinical Characteristics of Probands

The probands were all white and between 18 and 70 years of age (mean age, 46 years). The sociodemographic and clinical characteristics of the probands in the new proband groups based on presence or absence of alcoholism in the proband are presented in Table 2. There was a female-to-male ratio of approximately 60:40 by the design of the study. Although the probands with alcoholism were

Table 3.—Rates of Disorders Among Relatives of Probands

Proband Group	No. of Relatives	Rates/100, Disorders in Relatives			
		Major Depression*	Alcoholism†	Any Anxiety*	Antisocial Personality*
Normal	521	5.6	9.0	5.4	0.6
Depressed	810	14.9	14.4	12.8	3.8

*$P<.001$.
†$P<.01$.

Table 4.—Rates of Disorders Among Relatives by Presence of Alcoholism in Probands

Proband Group	No. of Relatives	Rates/100, Disorders in Relatives			
		Major Depression	Alcoholism	Any Anxiety	Antisocial Personality
Normal	521	5.6	9.0	5.4	0.6
Depression, no alcoholism	692	13.4	11.9	11.7	2.6
P, v normal	. . .	<.001	NS	<.001	<.001
Depression + alcoholism	118	23.7	29.7	19.5	10.2
P, v depression, no alcoholism	. . .	<.01	<.001	<.05	<.001

Table 5.—Rates of Disorders Among Interviewed Relatives by Presence of Alcoholism in Proband

Proband Group	No. of Relatives	Rates/100, Disorders in Relatives			
		Major Depression	Alcoholism	Any Anxiety	Antisocial Personality
Normal	137	10.2	16.1	14.6	1.5
Depression, no alcoholism	215	19.5	16.7	27.4	5.1
P, v normal	. . .	<.001	NS	<.001	<.001
Depression + alcoholism	48	35.4	39.6	43.8	16.7
P, v depression, no alcoholism	. . .	<.01	<.001	<.01	<.001

Table 6.—Ratio of Hazards of Disorders Among Relatives by Presence of Alcoholism in Proband (N = 1,331)

Proband Group	Diagnoses in Relatives, Ratio of Hazards* (95% Confidence Limits)/*P*		
	Major Depression	Alcoholism	Any Anxiety
Depression, no alcoholism *v* normal	3.62 (1.94-6.80)/<.001	1.36 (0.79-2.32)/NS	2.62 (1.35-2.13)/<.01
Depression + alcoholism *v* depression, no alcoholism	1.78 (1.16-2.71)/<.01	2.80 (1.88-4.16)/<.001	1.67 (1.31-2.13)/<.05

*Ratios were controlled for the significance of effects of interview status, sex of the relative, sex of the proband, and the year of birth of the relative.

younger than the other probands, they did not differ significantly from the other depressed probands on any of the other demographic or clinical variables. Likewise, the male and female probands within the group of alcoholics did not differ significantly on any demographic or clinical variables.

Rates of Disorders Among Relatives

The unadjusted rates of psychiatric disorders in the relatives are presented in Table 3. Rates of all disorders were significantly higher in the relatives of depressed *v* normal probands, with relative risks ranging from 1.6 for alcoholism to 6.3 for antisocial personality. When the group of depressed probands was broken down by the presence or absence of alcoholism (Table 4), rates of major depression, any anxiety, and antisocial personality were significantly higher among relatives of probands with depression without alcoholism compared with normal subjects, but rates of alcoholism were not different between the two groups.

The rates of all disorders were further increased among relatives of probands with depression and alcoholism compared with relatives of probands with depression only. This indicates that the increased rates of alcoholism among relatives of depressed probands can be accounted for by the presence of alcoholism in the proband. Table 5 shows that these effects were even more pronounced if the rates among relatives who were directly interviewed were examined.

Although there was an average of a twofold increase in the absolute rates of illness among interviewed relatives, the relative differences between the groups remained consistent. Similarly, when the rates of disorders were examined separately for male and female relatives, the relative differences between the groups remained the same. The only exception to this finding was that female relatives of probands with alcoholism did not have an increased rate of antisocial personality compared with female relatives of probands with depression only, whereas male relatives of depressed probands with alcoholism had a sixfold greater risk than male relatives of probands with depression only. Across all proband groups, female relatives had increased rates of major depression and anxiety disorders, whereas male relatives had higher rates of alcoholism and antisocial personality.

The results of the proportional hazards analysis that compared the age-specific incidence of the disorders in the groups of relatives while simultaneously controlling for the effects of interview status, sex of relative, year of birth of relative, and sex of proband, are presented in Table 6. Antisocial personality was not included in this analysis because the onset of this disorder is assumed to occur before the age of 18 years. Hence, in our sample, all of the relatives

Table 7.—Rates of Major Depression and Alcoholism Among Relatives by Presence of Alcoholism in Probands (N = 1,331)

Proband Group	No. of Relatives	Rates/100 Among Relatives		
		Depression Only	Alcoholism Only	Depression + Alcoholism
Normal	521	3.5	6.7	2.1
P, v depression, no alcoholism	. . .	<.001	NS	NS
Depression, no alcoholism	692	11.0	9.3	2.5
P, v depression + alcoholism	. . .	NS	<.01	<.001
Depression + alcoholism	118	12.7	17.8	11.0
P, v normal	. . .	<.001	<.001	<.001

would have passed through the age of risk and no age correction would be necessary. Table 6 confirms the results of Table 4. The ratio of hazards comparing relatives of probands with depression only *v* relatives of normal subjects is 3.6 times higher for major depression and 2.6 times higher for any anxiety disorder, both of which are highly significant. The ratio of hazards for alcoholism was 1.36, which is not significantly different between the two groups.

The ratios of hazards for all three disorders were significantly higher for the relatives of probands with secondary depression compared with relatives of probands with depression and no alcoholism. It is interesting to note that the age-specific incidence of alcoholism is nearly three times higher in the relatives of the alcoholics compared with relatives of depressed probands without alcoholism.

In all of the analyses, there were strong main effects for the interview status, sex of relatives, and year of birth of the relatives, with interviewed relatives in later birth cohorts having higher rates than noninterviewed, older relatives. Female relatives had greater rates of major depression and any anxiety, whereas male relatives had higher rates of alcoholism. The sex of the proband and two-way interactions among the preceding variables were not significant in any of the analyses.

Because there was such a high degree of assortative mating in the proband generation but not in the parental generation in this sample,[9] the preceding analyses were conducted using only the parents and siblings of probands, and similar results emerged.

To examine the effect of the non-independence of observations that were obtained from several members of the same family, the data were also reanalyzed for one random sibling per family. The significance of the results was similar to those obtained for the entire group of first-degree relatives.

Because the transmission of alcoholism seemed to be associated with the group of depressed probands with alcoholism, combinations of depression and alcoholism among the relatives were examined (Table 7). In comparing the first two rows, we found that the only diagnosis that was significantly increased among the relatives of probands with depression only was depression only. Rates of alcoholism only and depression plus alcoholism were not increased among the relatives of the depressives with no alcoholism compared with relatives of normal control subjects.

A comparison of the second two rows reveals that rates of alcoholism alone and alcoholism plus major depression were significantly greater among relatives of the alcoholic probands compared with the nonalcoholic probands. Rates of depression alone were not further increased among relatives of the secondary alcoholic probands. The greatest increase in risk to relatives was seen in the fourfold increase in the risk of depression plus alcoholism among the relatives of the probands with depression plus alcoholism compared with the probands with depression only. This suggests that there may be some specificity in the transmission of the combination of depression and alcoholism.

In summary, when compared with normal control subjects, relatives of probands with depression only had increased risk of depression only, whereas relatives of probands with depression plus alcoholism had an increased risk of both disorders alone and in combination.

Table 8.—Additional Severity Factors Among 19 Probands With Alcoholism

Severity Factor	No. of Probands (%)
Age of onset of major depression <40 yr	18 (95)
Suicidal ideation or attempts	17 (89)
Ideation only	13 (68)
Attempts	4 (21)
Anxiety disorder, all	13 (68)
Agoraphobia	3 (16)
Panic disorder	5 (26)
General anxiety disorder	5 (26)
Anxiety disorder + suicidal ideation or attempts + age of onset <40 yr	12 (63)

Additional Severity Factors Among Probands With Secondary Alcoholism

Because there was a considerable degree of overlap in severity factors among the probands with alcoholism, combinations of other known severity factors among the probands with alcoholism were examined.[13,14,22-24] Table 8 shows that most of the depressed probands with alcoholism had an early age at onset of major depression (95%), suicidal ideation or attempts (89%), or an anxiety disorder (68%), and 63% had all of these characteristics.

We then compared the rates of illness in the relatives of alcoholic probands who had all of the preceding factors with the relatives of depressed probands who had all of the preceding factors except alcoholism, to determine whether the increased risk of alcoholism and anxiety disorders could be attributed to some factor in the probands other than the alcoholism per se. The results of this analysis are presented in Table 9. The relatives of the probands with alcoholism and the other severity factors still had increased ratios of hazards of both alcoholism and anxiety disorders compared with the relatives of probands with all of the severity factors except alcoholism. Rates of major depression, however, were not different between the two groups. Thus, the increased risk of both alcoholism and anxiety disorders in relatives of alcoholic probands could be attributed to the alcoholism or some component of the alcoholism, rather than to the other known severity factors that may have been present in this group.

Following is a summary of our results.

1. Rates of major depression, alcoholism, anxiety disorders, and antisocial personality were higher among relatives of depressed *v* normal probands.

2. Relatives of probands with depression and no alcoholism had increased rates of major depression, anxiety disorders, and antisocial personality compared with relatives of normal probands, but

Table 9.—Ratio of Hazards of Diagnoses Among Relatives of Probands With Depression, Anxiety Disorder, and Suicidal Ideation and/or Attempts by Presence of Alcoholism in Proband

Proband Group	No. of Probands	No. of Relatives	Diagnoses in Relatives, Ratio of Hazards* (95% Confidence Limits)/P		
			Major Depression	Alcoholism	Any Anxiety
Depression, anxiety, early onset, suicidal, alcoholism	12	67	1.19 (0.68-2.06)/NS	2.03 (1.22-3.34)/<.01	2.07 (1.15-3.75)/<.01
Depression, anxiety, early onset, suicidal, no alcoholism	47	283			

*Ratios were controlled for the significance of effects of interview status, sex of the relative, sex of the proband, and the year of birth of the relative.

rates of alcoholism were not different between the two groups.

3. Relatives of depressed probands with alcoholism were at increased risk for all disorders examined in this analysis, particularly alcoholism.

4. The group of relatives of probands with depression and alcoholism had an increased risk of alcoholism alone and alcoholism with major depression when compared with relatives of probands with depression only. There was no further increase in the risk of major depression only in the relatives of probands with alcoholism plus depression compared with the relatives of probands with depression only.

5. The increased risk of alcoholism and anxiety disorders in the relatives of the probands with depression plus alcoholism could be attributed to the alcoholism or some component of the alcoholism, rather than to other severity factors that may have been present in these probands.

COMMENT

The results of the present study confirm those of previous studies that have demonstrated that depression and alcoholism are not alternate manifestations of the same underlying disorder.[7,11] If this were the case, probands with depression only would be as equally likely to transmit alcoholism as are probands with depression plus alcoholism. Our findings indicate that depressives without alcoholism did not transmit alcoholism, and probands with depression and alcoholism transmitted both depression and alcoholism. This was also the conclusion of Cloninger et al,[7] who demonstrated the independence of transmission of alcoholism and depression in a sample of probands who were ascertained for alcoholism rather than for depression, as were the probands in the present study.

The extremely high rates of antisocial personality in the interviewed relatives of probands with alcoholism (16.7%) confirm the association between alcoholism and antisocial personality that has been reported in numerous studies.[25] A majority of relatives with antisocial personality (70%) also had alcoholism. Previous studies have suggested that the two disorders are etiologically independent.[25] However, there were too few individuals with antisocial personality alone to analyze the relationship of the disorders in our sample.

Despite the independence of transmission of these disorders (ie, depression, alcoholism, and antisocial personality), it is probable that there is familial clustering of social risk factors that are related to the development of these disorders. This clustering of sociocultural factors would explain the frequently observed association of these disorders. Thus, the findings of this study do not imply that the increased severity in the group of depressed probands with alcoholism as defined by rates of illness in family members can be attributed to genetic factors.

It was interesting that the increased risk of anxiety disorders in the relatives of the probands with alcoholism could be specifically attributed to the presence of alcoholism in addition to an anxiety disorder. Van Valkenburg et al[26] reported an increased risk of alcoholism in the first-degree relatives of probands with depression and anxiety disorders. It is possible that the alcoholism in our probands with alcoholism and anxiety disorders was a result of self-medication of symptoms of anxiety, which in their cases were severe enough to warrant diagnoses. Although the literature on this subject is not conclusive, there is some evidence of the anxiety-reducing function of alcohol.[27] However, because of the retrospective nature of our data and the small number of probands with alcoholism and no anxiety disorder, this relationship could not be examined further.

The results of the present study suggest that the relationship between alcoholism and depression needs to be more fully examined. The patterns within the families of depressed and alcoholic probands are consistent with the hypothesis that there is some specificity in the transmission of the two disorders. However, it is not clear whether the combination of the two disorders occurs more frequently than would be expected by chance. It may be that alcohol and depression are being transmitted independently in these families and that the occurrence of relatives with both diagnoses is what is to be expected by chance alone. However, it may be that alcoholism and depression are being transmitted together and that this represents a subtype of affective disorder or alcoholism. Additional data are needed to explore these questions. Specifically, we are currently analyzing the patterns of transmission in these families as well as in families in which the onset of alcoholism occurred before the onset of the depression (our excluded probands). With these data we will be able to more carefully address the question of the possible causative relationship of these two disorders.

A major implication of the present study is that examining the combinations of diagnoses in patients is of major importance in defining the heterogeneity of diagnostic categories. Because the risk of numerous disorders was significantly higher among relatives of probands with depression plus alcoholism compared with relatives of probands with depression only, important sources of variation in the transmission of these disorders may be obscured by subsuming these two groups of probands in the single diagnostic category of major depression. This was the conclusion of Leckman et al,[13] who demonstrated the importance of not imposing hierarchical schemes in making diagnoses of depression and anxiety disorders. Family studies provide one valuable means of elucidating these issues.

This research was supported in part by Alcohol, Drug Abuse and Mental Health Administration grant MH 28274 from the Center for Epidemiologic Studies and from the Center for Studies of Affective Disorders, National Institute of Mental Health, Rockville, Md.

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