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Alcoholism and panic disorder: co-occurrence and co-transmission in families

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Summary. The co-occurrence of alcoholism and anxiety disorders in epidemiological and clinical samples is well established. Self-medication of anxiety disorder probands with the anxiolytic substance alcohol might be one reason for this association. Common susceptibility factors of both disorders might be alternative explanations. Controlled family studies recruiting probands with panic disorder and alcoholism are powerful tools to answer this question. A family study of this kind, however, is not available. The present study investigated 113 families of probands with either panic disorder or alcoholism or both (but without affective or psychotic disorders) and 80 families of healthy controls in order to estimate the degree of co-occurrence of the two disorders in non-treated samples of relatives and to explore the magnitude of overlap between susceptibility factors of the two disorders. The co-occurrence of the two disorders was relatively rare in all samples of families under study. Overlap of susceptibility factors was demonstrated by an elevated risk of alcoholism in relatives of probands with panic disorder.

Key words: Alcoholism – Panic disorder – Family studies – Co-occurrence – Co-transmission

Introduction

Clinical and epidemiological samples have shown an excess of co-occurrence of anxiety disorders and alcoholism as compared with a random pattern of co-occurrence (Meyer and Kranzler 1989). In this context, comorbidity or, synonymously, co-occurrence means that a subject has fulfilled the diagnostic criteria for two disorders during lifetime, either within separate episodes of illness or, by neglecting diagnostic hierarchies, within the same episode of illness. A differential treatment seeking behaviour (Berkson's bias) might explain the co-occurrence of the two syndromes in treated samples, but not the co-occurrence in general population samples (Regier et al. 1990). Here the alternative explanations are:

1. Causal links between the two syndromes (one syndrome might provoke the other syndrome as a complication).
2. The combination of both syndromes indicates the presence of a distinct disorder and not just the combination of two distinct disorders.
3. The two syndromes might share common susceptibility factors.

Previous studies have discussed this association primarily under the perspective of the causal link hypothesis (hypothesis 1) by reference to a tension reduction or a self-medication theory. The tension reduction theory dating back to Conger (1956) proposes that alcohol reduces tension and that people drink in order to experience relief from tension. A recent study provided empirical evidence that this mechanism is especially operating in subgroups of male subjects, but less so in female subjects (Cooper et al. 1992). As anxiety includes the experience of tension, self-application of alcohol might be the consequence. Alcohol also reveals an anxiolytic potency via a regulation of the benzodiazepine/GABA receptor complex what might additionally reinforce alcohol consumption in subjects with anxiety disorders. This mechanism suggests self-medication as a subsidiary mechanism. The other two hypotheses (2 and 3) have received less attention. At present, it is not clear which of the three putative hypotheses is the most valid.

Since alcoholism (review by Merikangas 1990) as well as panic disorder (Crowe et al. 1983; Noyes et al. 1986) have been shown to be familial, controlled family studies including probands with any of the two syndromes and with the combination of them can contribute to the judgement of the merits of the three alternatives. The first hypothesis also proposes an excess prevalence of alcoholism in families of probands with panic disorder and vice versa; but this excess prevalence is exclusively due to an excess of comorbid cases in affected relatives. The second hypothesis predicts an excess co-occurrence

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of the two syndromes in relatives especially under the condition that the proband presents with both syndromes. The last alternative (hypothesis 3) predicts that alcoholism in the absence of panic disorder is aggregating in families of probands with panic disorder, even if the proband is not comorbid for alcoholism, and vice versa. This prediction is not compatible with any of the other two hypotheses.

Family studies addressing issues of the relationship between two or more syndromes require an appropriately broad range of sampling, and they require that the diagnostic assessment in probands is blind to and independent of the diagnostic assessment in relatives and vice versa. The Yale family study was the first to investigate the relationship between anxiety disorders and alcoholism (Merikangas et al. 1985); it was concluded that there is an overlap of susceptibility factors (Merikangas et al. 1992). However, valid conclusions from this study with regard to alcoholism and anxiety disorders are limited, as the sample of recruited probands was restricted to major depression and controls only. Appropriate family studies including systematically recruited probands with anxiety disorders as well as probands with alcoholism also in absence of comorbidity with other syndromes are currently not available.

Methods

Probands

The clinical sample of 113 probands in this study is part of an extended sample of probands ($n = 726$), consecutively admitted as in- and outpatients of the psychiatric hospital of Mainz, who had at least one first-degree relative willing to be interviewed directly. These probands were not preselected by diagnoses. Probands of this sample, suffering from panic disorder with or without agoraphobia (RDC) or alcoholism (RDC), were selected for the present study. The following subgroups of probands were excluded:

1. Probands with a lifetime diagnosis of schizophrenia, other psychotic disorders, bipolar disorder, or unipolar depression.
2. Probands receiving the diagnosis of alcoholism and reporting anxiety syndromes only during or subsequent to periods of alcohol or drug abuse were excluded. The rationale for this restriction is that under this condition it cannot be ruled out with sufficient certainty that the anxiety syndromes are due to the alcohol or drug abuse which would rule out the diagnosis of an anxiety disorder according to most of the diagnostic manuals. As a consequence, this study includes only probands with secondary alcoholism as probands suffering from a combination of alcoholism and panic disorder.
3. Probands with alcoholism without panic disorder but with attacks or with agoraphobia or with social phobia were excluded. The rationale for this exclusion is that probands with these anxiety syndromes might carry an elevated risk for panic disorder, even in absence of the panic disorder diagnosis. Probands with generalized anxiety disorder were not excluded, as Noyes et al. (1986) have shown independence of familial transmission from panic disorder.
4. Probands with panic disorder and substance abuse but without alcoholism were excluded.

Table 1 shows the numbers of co-operative patients and controls with at least one living first-degree relative who could be asked to participate (contacted probands). In most families that were approached at least one relative was willing to participate; only under this condition were a proband and his/her family included.

The sample of control probands was recruited from the general population. The exclusion criterion for being a proband was that no first-degree relative was willing to be directly interviewed. Probands were contacted by a marketing company for participation. Mean age and gender were matched to a random sample of patients enrolled as probands in this study. Among 130 co-operative probands with an available first-degree relative, 109 had at least one relative who consented to be directly interviewed. Control probands were selected independently of their psychiatric status and were matched by age, sex, educational status, and area of residence to a random sample of patients who were recruited as probands. Within the particular strata, the controls were selected in a representative manner. Eighty control probands did not receive a lifetime diagnosis of any RDC disorder by direct diagnostic interview; the families of these 80 healthy control probands were considered as controls.

Relatives

All living first-degree relatives of both proband groups were contacted and asked for participation. More than 78% of the living first-degree relatives of patients in any proband group were interviewed directly, either at home or in hospital (Table 1). Relatives were interviewed bindly with regard to the proband's diagnosis, and vice versa. Relatives were also asked for the history of psychi-

Table 1. Characteristics of family samples under study defined by types of probands

	Proband groups			
	Alcoholism only	Alcoholism and panic disorder	Panic disorder only	Healthy controls
Number of probands				
Contacted[a]	56	35	46	104
Included	40	24	40	80
Sex ratio (male, %)	75	70	63	58
Age (mean)	35.9 years	34.2 years	38.8 years	39.2 years
First-degree relatives				
Number of all relatives	228	98	174	309
Number of interviewed relatives	150	60	119	221
Sex ratio (male, %)	42	52	50	46
Age (mean)	39.2 years	41.2 years	40.4 years	40.0 years

[a] (i.e. with at least one first-degree relative who could be approached)

atric disorders of those of the proband's relatives who were either dead, who refused or who were not able to participate in this study personally. In order to keep the blind, relatives were not asked for psychiatric syndromes in probands, and probands were not asked for psychiatric disorders in their relatives. Table 1 reports the characteristics of the sample under study.

Psychopathological assessments

The diagnostic assessment followed the lines proposed by Weissman et al. (1986). The SADS-LA (Schedule for Affective Disorders and Schizophrenia, Lifetime Version, Modified for the Study of Anxiety Disorders; Mannuzza et al. 1986) was administered to probands and directly interviewed relatives. The SADS-LA pays extensive attention to anxiety disorders and refers simultaneously to RDC, DSM-III, and DSM-III-R diagnoses. Anamnestic information on other relatives was received by using the family history approach (Mannuzza et al. 1985) that focuses on major diagnostic categories, including panic disorder, agoraphobia, and alcoholism, but neglects other anxiety disorders which are therefore excluded from this report. The interviewers were carefully trained physicians, psychologists or advanced medical students with a minimum of clinical experience. Each had at least 15 training sessions. The test-retest reliability of the individual diagnoses was tested before starting the study and turned out to be sufficient (kappa < 0.75) for all diagnostic categories used in this study.

Final diagnostic assessments were based on best estimate diagnoses (Leckman et al. 1983): the interview forms, the family history information obtained by relevant others, and the medical records were joined together in a final diagnostic judgement by an independent experienced clinician. Several diagnostic manuals were used; this paper reports diagnoses by RDC. The diagnostic category of panic disorder includes the definite as well as the probable level of diagnostic certainty as defined by RDC, that is at least three panic attacks within 3 weeks. This definition is identical to the DSM-III definition, and most publications are based on it. The diagnosis of alcoholism required the full syndrome as defined by RDC.

Statistical methods

Proportional hazard models were applied to explore to which extent the occurrence of a particular disorder in relatives is influenced by the proband's diagnosis. Age at onset of a disorder was introduced as the dependent variable; further co-variates were entered to control for the influence of modifying variables in relatives (age, gender) and probands (the same). Disorders in probands were introduced as the independent variable. This type of analysis was conducted separately in three samples: relatives of probands with alcoholism only or relatives of healthy control probands, relatives of probands with alcoholism associated with panic disorder or relatives of healthy control probands, relatives of probands with panic disorder only or relatives of healthy control probands. The BMDP software program was applied (Dixon et al. 1990).

Results

Tables 2 and 3 describe the crude lifetime prevalence rates (not adjusted for age) for panic disorder and alcoholism in the four comparison groups. These prevalences of panic disorder and alcoholism in the sample of control families fit well into the range defined by previous epidemiological surveys and reports on control groups in family studies (Wittchen et al. 1991; Robins et al. 1984); this similarity supports the validity of the control sample.

Table 2. Lifetime prevalence rates (%) of alcoholism and panic attacks in directly interviewed first-degree relatives by probands' group

Syndrome diagnosis in relatives	Interviewed relatives by probands' group			
	Alcoholism only ($n = 150$)	Alcoholism and panic disorder ($n = 60$)	Panic disorder only ($n = 119$)	Healthy controls ($n = 221$)
Any alcoholism	17.3	13.3	13.6	6.8
Any panic attacks	10.0	28.3	21.8	5.0
Any panic disorder	4.0	8.3	6.4	1.8
Alcoholism without panic disorder	16.0	11.7	11.8	6.3
Alcoholism and panic disorder	1.3	1.7	1.8	0.5
Panic disorder without alcoholism	2.7	6.7	4.5	1.4

[a] *Not* adjusted for age

Table 3. Lifetime prevalence rates (%) of alcoholism and panic disorder in first-degree relatives (based on direct interview and on family history information) by probands' group

Syndrome diagnosis in relatives	Relatives by probands' group			
	Alcoholism only ($n = 228$)	Alcoholism and panic disorder ($n = 98$)	Panic disorder only ($n = 174$)	Healthy controls ($n = 309$)
Any alcoholism	15.4	16.0	12.1	5.8
Any panic disorder	3.5	8.0	6.3	1.6
Alcoholism without panic disorder	14.1	13.0	10.3	5.5
Alcoholism and panic disorder	1.3	3.0	1.7	0.3
Panic disorder without alcoholism	2.2	5.0	4.6	1.3

Table 4. Lifetime prevalence rates[a] (%) of alcoholism and panic disorder in first-degree relatives by sex and probands' group

Syndrome diagnosis in relatives	Relatives by sex and probands' group							
	Male relatives				Female relatives			
	Alcoholism only ($n = 111$)	Alcoholism and panic disorder ($n = 47$)	Panic disorder only ($n = 86$)	Healthy controls ($n = 148$)	Alcoholism only ($n = 117$)	Alcoholism and panic disorder ($n = 51$)	Panic disorder only ($n = 88$)	Healthy controls ($n = 161$)
Any alcoholism	23.7	25.5	18.6	10.1	6.8	7.8	5.7	2.7
Any panic disorder	1.8	8.5	4.7	1.4	5.1	7.8	8.0	1.9
Alcoholism without panic disorder	22.0	21.2	16.3	9.5	5.1	5.9	4.5	1.9
Alcoholism and panic disorder	0.9	2.1	2.3	0.7	0.9	2.0	1.1	0.8
Panic disorder without alcoholism	0.9	2.1	2.3	0.7	3.4	5.9	6.8	1.9

[a] *Not* adjusted for age

Table 5. Adjusted[a] odd ratios (relative risks with 95% confidence intervals) comparing rates of alcoholism and panic disorder in relatives of affected probands to relatives of healthy controls

Syndrome diagnosis in relatives	Relatives by probands' group		
	Alcoholism only	Alcoholism and panic disorder	Panic disorder only
Any alcoholism	3.3 (1.7, 6.6)**	3.0 (0.6, 8.3)*	2.2 (0.8, 4.4)*
Any panic disorder	2.0 (1.0, 3.7)*	4.8 (2.9, 7.9)**	4.0 (2.4, 7.2)**
Alcoholism without panic disorder	3.2 (1.3, 6.7)	2.7 (1.3, 5.6)	1.7 (1.0, 3.8)
Alcoholism and panic disorder	4.9 (3.1, 7.8)	8.2 (2.5, 18.4)	8.0 (3.0, 16.2)
Panic disorder without alcoholism	1.5 (0.7, 2.6)	3.6 (2.0, 5.9)	3.7 (1.1, 8.6)

[a] Adjusted for sex, age and interview status of relatives
* $0.01 < P \leq 0.05$; ** $P \leq 0.01$

It is apparent from Tables 2 and 3 that panic disorder as well as alcoholism are aggregating in families of probands with the same disorder independent of the definition of the disorder as pure types (i.e. panic disorder without alcoholism, alcoholism without panic disorder) or as broad diagnostic categories (neglecting comorbidity). It is particularly noteworthy that alcoholism without panic disorder is substantially more frequent among relatives of probands with panic disorder without alcoholism as compared to control families, and that panic disorder without alcoholism is more frequent among relatives of probands with alcoholism without panic disorder as compared to control families. Cases with the combined diagnosis (panic disorder and alcoholism) also aggregate in families of probands with the same condition, but the magnitude of the prevalence rates of this condition is very low in all comparison groups under study.

The sex-specific prevalence rates displayed in Table 4 propose that panic disorder (and especially panic disorder only) is more common among female as compared with male relatives, whereas alcoholism (and especially alcoholism only) is more frequent among male as compared with female relatives. These sex ratios are very similar across the four comparison groups of relatives defined by the probands' type. The co-occurrence of the two syndromes during lifetime reveals no clear male or female preponderance; this particular observation should be considered with caution because of the low prevalence rate of the comorbid condition among relatives in all comparison groups.

A putative reason for the excess alcoholism in families of panic disorder probands might be that anxiety disorders other than panic disorder are also aggregating in these families, which might give rise to secondary alcoholism; the family study by Miller et al. (1989) points in this direction. In Table 4, those hypothetical cases have been counted as "alcoholism only" cases. After extension of the diagnostic range of panic disorder by phobic disorders (with the exception of simple phobia and generalized anxiety disorder) and of alcoholism by any other kind of substance abuse as defined by RDC the results were similar to those obtained on the basis of the narrow diagnoses.

The cross-prevalences (i.e. risk of disorder A in relatives of probands with disorder B in relation to relatives of controls) of the pure types are clearly informative with respect to the extent of overlap of susceptibility factors between the two disorders. Among the relatives of probands with alcoholism alone, 21.5% received a diagnosis of substance abuse without panic or phobic disorder, 2.2% were diagnosed as substance abuse with panic or phobic disorder, and 3.5% of relatives had panic or a phobic disorder alone. For relatives of probands with panic disorder alone, the corresponding figures were 13.2%, 4.0% and 9.2%, and for relatives of healthy controls, 10.4%, 2.3% and 5.0%, respectively. The impact of a proband's "pure" panic disorder diag-

nosis on the diagnosis of "pure" alcoholism in relatives was explored by application of the Cox regression model. We obtained the following result (Table 5): the risk of alcoholism without panic disorder was significantly elevated among relatives of probands with panic disorder without alcoholism ($P = 0.05$ by proportional hazard model). However, the reciprocal relationship only showed a trend to being significant: although panic disorder without alcoholism was more frequent in relatives of probands with alcoholism without panic disorder than in relatives of controls, the relative risk was not significantly different from the balanced risk 1.0 ($P = 0.08$).

Discussion

Familiality of alcoholism and panic disorder

This study confirmed panic disorder to be familial, as had been previously reported by Crowe et al. (1983), Noyes et al. (1986), and Cloninger et al. (1981). However, there are also differences compared with these previous studies with regard to the degree of familial aggregation: Crowe et al. (1983) reported a substantially higher frequency of panic disorder (with and without agoraphobia) in families of panic disorder probands compared to our results. We found 5.7% compared with 17.3% (not age-corrected!) as reported by Crowe et al. (1983), whereas the risk in families of controls – despite the differences in recruiting the control families – was very similar (1.8% in our study and 2.1% in Crowe's study). However, the second family study on panic disorder and agoraphobia also conducted in Iowa (Noyes et al. 1986) reported a lifetime risk between 17 and 18% if definite as well as probable diagnoses of panic disorder were taken into account (Noyes et al. 1986). These rates were very similar to the lifetime risk of any type of panic attack found in our study (17.6%). Unfortunately, the figures for definite cases of panic disorder were not reported by Noyes et al. (1986) and the category of "probable" panic disorder was not precisely defined. Cloninger (1981) suggested that there might be a gender-specific familial aggregation of panic disorder with only female relatives of panic disorder probands at a very high and increased risk (lifetime risk 50%), whereas this disorder would not aggregate among male relatives; the present study found relative risks not to be a function of gender. This discrepancy might be explained by the relatively low frequency of panic disorder in males and the relatively low sample size in Cloninger's study, which reduces the chances of detecting an increased relative risk in male relatives.

This study also confirmed alcoholism to be familial, as was proposed by a series of previous family studies (review by Merikangas 1990). The ranges of prevalence rates of alcoholism in families of probands with alcoholism as well as in families of controls or the general population were very broad (Merikangas 1990). The rates reported in this study were lower than the corresponding rates in the most recent American studies using similar techniques (Reich et al. 1988; Robins et al. 1984). One major reason for this broad variation of prevalence rates might be different social or cultural factors operating in different populations (Helzer et al. 1990). Although the prevalence of alcoholism was substantially lower in females compared with males, the familiality indicated by the relative risk (compared with control samples) was observed to be similar in male compared with female relatives. This result is in agreement with most of the previous reports (Merikangas 1990).

The present study did not provide evidence that the co-occurrence of lifetime diagnoses of panic disorder and alcoholism defines a separate disorder in terms of familial transmission. Although the relative risk (compared with controls) of this condition was maximal in relatives of probands presenting with this combined diagnosis, the risk for panic disorder without alcoholism and for alcoholism without panic disorder was also elevated. The first observation argues for the combined diagnosis as a separate disorder, the second observation argues that the combined diagnosis represents the coexistence of two distinct disorders. These figures are most compatible with the view that the comorbid condition is heterogeneous in terms of familial aggregation: segregation as a separate disease in a subgroup of families and segregation as two different diseases in other families. However, the size of the sample of relatives of probands with both lifetime diagnoses was rather limited and, consequently, random fluctuation might have blurred the figures observed in this particular group of relatives.

Co-segregation of alcoholism and panic disorder

Are these two mutually exclusive categories of disorders separate disorders in terms of familial transmission? The examination of the cross-prevalences of pure subtypes of each disorder (i.e. prevalence of disorder A without B in relatives of probands with disorder B without A) are informative for answering this question. The present study indicated that the cross-prevalences of "pure" panic disorder as well as of "pure" alcoholism were higher by a factor of a least 2.0 compared with controls. This finding extends previous reports on excessive alcoholism in relatives of panic disorder probands (Crowe et al. 1983) and on excessive morbidity of anxiety disorders in the offspring of alcoholic probands (Earls et al. 1988; Sher et al. 1991). Our study also indicated that these elevations of cross-prevalences of pure types were not due to comorbidity of the two conditions in probands or in relatives. Although the relative risks were comparable, only the risk of "pure" alcoholism was significantly elevated in families of "pure" panic disorder probands; the lack of significance of the inverse relationship might at least partly be due to the relatively lower base rate of panic disorder, implying a reduction of the power to detect an elevation of the relative risk for this disorder.

The limited validity of diagnostic definitions has, however, to be taken into account: the boundaries of panic disorder and alcoholism as they are transmitted in families might not be identical with the diagnostic boun-

daries defined by diagnostic manuals. The familial liabilities to panic disorder and to alcoholism might be alternatively expressed either by other disorders or by syndromes not qualifying as psychiatric diagnoses. Under this assumption, (a) the subtypes "panic disorder only" and "alcoholism only" might wrongly include cases carrying the liability to both disorders, and (b) relatives with alternative expressions of the liability to any of the two disorders might wrongly be considered as unaffected. It has been shown that the excess morbidity of alcoholism in relatives of panic disorder probands will hold if the occurrence of phobic disorders (with the exception of simple phobia), of other substance abuse disorders, and of panic attacks not qualifying as panic disorder is taken into account. In the light of this observation, it is unlikely that the main link between panic disorder and alcoholism is established by self-medication or by the tension-reducing potency of alcohol. Sharing of common familial factors is likely to be the case. This suspected overlap of familial factors may be reflected in a common pathophysiological basis of alcoholism and panic disorder for whom serotonergic mechanisms are a main candidate (Tollefson 1991).

Limitations

The degree of certainty of this conclusion is, however, limited: anxiety states (other than panic attacks) below the diagnostic threshold might also aggregate in families of panic disorder probands and might provoke excessive drinking resulting in alcoholism. This possible explanation cannot fully be explored, as symptoms of psychic or somatic anxiety or nervousness were reported by more than 90% of subjects with alcoholism; most of these symptoms emerged during withdrawal states, but putatively also earlier. The definite exclusion of alcoholism as self-medication of anxiety states would therefore require information on the exact temporal sequence of emerging anxiety-related symptoms and changes in drinking behaviour; knowledge of the temporal sequence of the manifestations of anxiety disorders and of substance abuse disorders would not be sufficient. This detailed information cannot be obtained with sufficient precision by retrospective assessment. Only family studies with a prospective component can address this problem; this kind of study is currently not available.

A limitation of this study is that it relies on the RDC definition of alcoholism. The underlying concept is that alcoholism provokes psychosocial and social problems which are the guide to the diagnosis. RDC does not attempt to separate a dependency syndrome from an alcohol abuse syndrome. Therefore, we cannot decide on the basis of the available data if the aggregation of alcoholism in families of panic disorder probands is just an aggregation of alcohol abuse or if it is also an aggregation of alcohol dependence.

Conclusion

The relative risks of alcoholism as well as of panic disorder were elevated by a factor of 3.0 or higher in relatives of probands with the same disorder as compared to controls. The familiality of both disorders indicated by the relative risks was substantially higher than for unipolar depression for whom relative risks of about 2.0 were found in recent family studies (Maier et al. 1990; Weissman et al. 1982). Previous research has demonstrated that genetic factors account, at least partly, for the familiality of alcoholism and panic disorder (Torgersen 1983; McGue et al. 1992; Kendler et al. 1993); additional environmental factors are relevant, as perfect concordance between monozygotic twins is lacking. These and other available twin or genetic studies are not informative with regard to the question whether alcoholism and anxiety disorders might share common genetic or environmental factors of aetiological relevance. While the present family study cannot specifically distinguish between genetic and environmental sources, it is proposed that the genetic and/or environmental origins of the two disorders are linked.

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