The Familial aggregation of panic disorder by source of proband ascertainment

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Estimates of familial aggregation of psychiatric disorder obtained from relatives of probands ascertained in treatment settings may differ from estimates obtained from relatives of probands ascertained from the general population. In this paper we investigate this hypothesis for panic disorder, by comparing the degree of familial aggregation of panic disorder in relatives of probands with panic disorder ascertained from either a specialty anxiety clinic, a specialty depression clinic or a population survey, respectively. Results for panic disorder do not suggest that familial rates are associated with source of proband ascertainment. Results show that the rates of panic disorder in relatives were similar by proband source. This suggests that familial rates of panic disorder are not associated with proband ascertainment and that selecting probands from treatment clinics rather than from the general population does not necessarily lead to greater estimates of familial aggregation of panic disorder. Further research is needed to determine if this finding can be generalized to other psychiatric disorders.

Keywords: Familial aggregation – Panic disorder – Proband ascertainment

INTRODUCTION

The comparability of findings on the nature and correlates of psychiatric disorder in individuals identified in treatment settings, with those identified in general population surveys, is a topic that has received growing attention in recent years (Sashidharan *et al.*, 1990; Costello, 1990; Wittchen *et al.*, 1991). The importance of comparing and integrating findings from field surveys with those from treatment settings, because only a small proportion of those with psychiatric disorders are treated, has been noted by many of these authors. These issues would seem to be especially important when estimating the degree of familial aggregation of such disorders. However, the comparability of findings on the extent of familial aggregation observed in relatives of probands ascertained in treatment settings, with that of relatives of probands ascertained through general population surveys, has not, to our knowledge, been studied previously.

It has been hypothesized that familial aggregation in relatives of probands ascertained in treatment settings could be greater than that in relatives of probands ascertained from population surveys for at least three reasons.

(1) Probands ascertained in treatment settings may have a more severe form of the disease than probands ascertained in a general population survey. If the more severe form of the disease is more likely to be genetically transmitted, we would expect the familial aggregation of the disorder to be stronger in relatives of treated probands.

(2) Probands may go for treatment because several of their family members are also ill and are unable to take care of them.

(3) There may be a greater awareness of the disorder among family members and thus a greater likelihood of family members reporting symptoms of disorder, if a proband has already sought treatment.

If these hypotheses are indeed true, then estimates of familial aggregation obtained from studies using probands ascertained in treatment settings would be greater than the degree of familial aggregation observed in the general population.

The purpose of this paper was to determine whether the source of proband ascertainment was associated with rates of panic disorder in a family study, by comparing the familial aggregation of panic disorder in probands with panic disorder ascertained through two different treatment clinics, i.e. a specialty anxiety clinic and depression clinic or through a

population survey. We will use data from a recently completed family study to determine the relationship between panic disorder and major depressive disorder (MDD) to make these comparisons. We will compare the familial aggregation of panic disorder in relatives of probands with panic disorder both with and without MDD, by source of proband ascertainment.

METHODS

Study design
The study methodology has been described in detail by Weissman *et al.* (1993). The overall purpose of this study was to obtain comprehensive data by direct interview and family history, from multiple informants when available, on the first-degree relatives of probands with early onset ($\leqslant$ 30 years) major depression, panic disorder with and without MDD, and a normal, never mentally ill control group.

Probands were ascertained from two sources: speciality clinics at Yale University, the Connecticut Mental Health Center (Anxiety Research Clinic and the Depression Research Unit), and the New Haven site of the Epidemiologic Catchment Area (ECA) study. By design, about two-thirds of the ill probands were selected from treatment clinics, one-third from the ECA, and all normal control probands were ascertained exclusively from the ECA.

Proband selection
The ECA is a five site epidemiologic study of the prevalence and incidence of specific mental disorders in a probability sample of adults living in the community. The ECA probands came from the New Haven site, which included the Standard Metropolitan Statistical Area (SMSA; Robins and Regier, 1991). Probands were selected to be white, between 18 and 70 years of age, and initially meet the diagnostic criteria of one of the four cells, i.e. early onset ($\leqslant$ 30 years) MDD, panic disorder with and without MDD and never mentally ill. All came from the same geographic area (New Haven, Connecticut SMSA). Similarly probands were selected who were white and between the ages of 18 and 70 from separate Anxiety and Depression Clinics. Consecutive samples from the ECA and from the clinics who initially met the inclusion criteria were sampled and re-interviewed blindly as to their original clinic or ECA diagnosis by a member of the research team using the Schedule for Affective Disorders and Schizophrenia Lifetime Version for Anxiety Disorders (SADS-LA), which inquired about all major psychiatric disorders and

included details on the anxiety disorders. The SADS-LA generated Research Diagnostic Criteria (RDC) and was modified to also make DSM-III and DSM-III-R criteria. Persons were accepted as probands if they met the diagnostic and demographic inclusion criteria, described in detail in the next section, on re-interview and agreed to participate. Acceptance into the study was done blind to the subject's willingness to have family members interviewed as well as to family size or diagnoses of family members.

Consecutive samples of clinic probands (143 and 149 from the Anxiety and Depression Clinics, respectively) were screened and directly interviewed using the SADS. The refusal rate was 22% and 21%, respectively. Those meeting cell criteria who agreed to participate were accepted into the study. Ill probands from the ECA (refusal rate of 24%) were group matched as far as possible by age and sex to an ill proband in the same diagnostic category from the treatment clinics. There was only one proband per family in each of the four cells.

Diagnostic criteria of probands
Probands with any of the following diagnoses were excluded from all groups: schizophrenia, mania, Briquet's, antisocial personality disorder, and anorexia. The initial exclusionary criteria of alcohol and drug abuse for all proband groups were dropped due to the scarce number of probands without these conditions; thus, alcoholism and drug abuse were not exclusionary diagnoses if they were secondary to the primary diagnoses or were primary but mild, or if probands had a substantial time period of recovery before the onset of inclusion diagnosis. The primary/secondary distinction was based on chronology. In this paper, we are focusing exclusively on probands with panic with or without MDD. Consequently, only specific diagnostic criteria for this proband group will be described; probands with early onset MDD ($\leqslant$ 30 years) without panic, and never mentally ill probands will not be discussed further.

Panic Disorder with or without MDD. DSM-III panic disorder based on the SADS-LA interview was required. DSM-III criteria differ from RDC in that the latter requires six panic attacks in 6 weeks, whereas the former requires three attacks in 3 weeks. The DSM-III criteria were used for other anxiety disorders as well. The modified RDC (described above) was used for MDD, and detailed information on age of onset was obtained. In addition to the exclusion criteria applied to all probands, the probands in the group categorized as having panic disorder without MDD, had no evidence by any diagnostic criteria of

MDD at any level of certainty ever either preceding, concomitant with, or following panic disorder.

Assessment of relatives

All first-degree relatives were enumerated systematically from the proband using the Pedigree Collection Form (Thompson *et al.*, 1980); permission for contact with relatives was obtained from the proband. Direct interviews using the SADS-LA, either in person or by telephone, were carried out with all consenting relatives. In addition, family history information on first-degree relatives was obtained from all probands and interviewed relatives using a modified Family History Method for RDC (FH-RDC) initially developed by Andreasen *et al.* (1977). An earlier version of this modification was used in previous family studies by Weissman *et al.* (1984), and a further revision has been made by Mannuzza *et al.* (1986). Relatives about whom family history information was to be obtained were listed individually by name on the Pedigree Collection Form, with the relationships reoriented to the particular informant. All assessments were performed by clinically trained interviewers blind to proband diagnoses.

Best estimate diagnoses

Best estimate diagnoses, based on all information available concerning each proband and relative, were made by a psychiatrist of PhD clinical psychologist blind to proband diagnosis, unaware of whether the subject was a proband or a relative, and not involved in the data collection. Diagnoses were made according to RDC (Spitzer *et al.*, 1978), DSM-III and DSM-III-R (American Psychiatric Association, 1987) criteria, and assigned one of three levels of certainty: possible, probable or definite (Leckman *et al.*, 1982). Age of onset and severity of impairment due to each disorder were also estimated. Probands whose best estimate diagnoses were not consistent with the original diagnostic category assigned were either formally reassigned or excluded without knowledge of the data on relatives as follows: if the proband met diagnostic criteria for a different cell he/she was assigned to that specific cell; if the proband did not meet diagnostic criteria for a different cell or had exclusionary diagnoses, he/she was excluded.

Final sample of probands and relatives

In this report we have used the proband diagnostic system described above and we present DSM-III diagnoses in relatives. The composition of the final sample of probands and their relatives is shown in Table I. This sample consisted of 30 probands who had panic disorder without MDD (of these, seven probands were ascertained through the ECA and 23 probands were ascertained through the Anxiety Clinic), and 77 probands who had panic disorder with MDD (13 probands from the ECA, 52 probands from the Anxiety clinic, and 12 probands from the Depression Clinic).

A total of 141 first-degree relatives of probands who had panic without MDD and a total of 442 first-degree relatives of probands with panic and MDD were assessed. Fifty-two per cent of the first-degree relatives of panic without MDD probands and 40% of the first-degree relatives of panic with MDD probands were directly interviewed. Family history information from two or more relatives was available for 79% of relatives of probands without MDD, and 80% of relatives of probands with MDD.

Statistical methods

Statistical comparisons by source of proband ascertainment were performed on continuous variables by *t*-tests or one-way analysis of variance as dictated by the number of groups being compared. Chi-square tests were used to compare categorical variables when sample sizes were moderate or large, and Fisher's exact tests were used when sample sizes were small. Logistic regression analyses were performed, when the outcome variable was categorical and comparisons among source of proband ascertainment were made, controlling for potential confounding variables.

Implicit in the analyses reported in the sections that follow is that familial aggregation of a disorder is measured here by comparing rates of disorder in relatives of specified proband groups with the disorder to rates of disorder in relatives of proband groups without that specific disorder. Thus, in order for the use of treated probands to lead to overestimation of familial aggregation, the rates in relatives of treated probands must be greater than the rates in relatives of probands ascertained through the general population survey.

RESULTS

Proband characteristics by source of proband ascertainment

The original study design consisted of two mutually exclusive categories of panic probands, namely probands who had panic with or without major depression. In order to fully exploit this study design we have compared clinical and demographic characteristics of probands by source of proband ascertainment, first within these mutually exclusive categories

TABLE I. Number of probands and relatives by proband diagnosis and source of proband ascertainment

	Panic without MDD		Panic with MDD		
	Anxiety		Anxiety		Depression
	ECA	Clinic	ECA	Clinic	Clinic
No. of probands	7	23	13	52	12
No. of relatives	33	108	73	304	65

of panic disorder, and then where feasible across these categories.

Comparisons of demographic and clinical characteristics of probands by source of ascertainment are presented in Tables II-IV. These comparisons are provided to allow us to determine whether these characteristics are differentially distributed across these proband groups. If these proband characteristics, some of which measure the level of severity of the disorder, have differential distributions across

these groups, it is possible that they could account for differences found in rates of panic disorder in relatives.

Probands with panic disorder without major depression. A comparison of the socio-demographic characteristics of probands with panic disorder without MDD by source of proband ascertainment is shown in Table II. Although all probands ascertained through the ECA were female, and these probands are older than those ascertained through the Anxiety Clinic, the difference in distribution of gender was found to be only marginally significant statistically.

With the exception of the number of panic symptoms during the worst episode, which was marginally significant, there were no statistically significant differences with respect to clinical characteristics of probands or their treatment-seeking behavior by source of proband ascertainment. Note that outpatient treatment is defined as "seeking help from a doctor or other professional". The manner in which this question was framed does not allow us to differentiate between primary care physicians and psychia-

TABLE II. Demographic and clinical characteristics of probands with panic without MDD by source of proband ascertainment

	ECA ($n = 7$)	Anxiety Clinic ($n = 23$)	p value
Sex			
Male [n (%)]	0 (0%)	10 (43.5%)	0.06
Female [n (%)]	7 (100%)	13 (56.5%)	
Age (years)	52.95	40.42	N.S.
Mean (S.D.)	(16.88)	(9.56)	
Social class	2.67	3.26	N.S.
Mean (S.D.)	(1.63)	(1.01)	
Age of panic onset	30.43	26.83	N.S.
mean (S.D.)	(11.15)	(8.2)	
Impairment (panic)			
None/mild	5 (71.4%)	13 (56.5%)	N.S.
moderate/severe	2 (28.6%)	10 (43.5%)	
No. of panic symptoms during worst episode	6.43	4.22	0.06
mean (S.D.)	(2.76)	(2.56)	
Co-morbidity			
Social phobias	2 (28.6%)	4 (17.4%)	N.S.
Simple phobias	2 (28.6%)	4 (17.4%)	N.S.
Alcohol abuse/dependence	1 (14.3%)	2 (8.7%)	N.S.
Drug abuse/dependence	0 (0.0%)	2 (8.7%)	N.S.
Outpatient treatment (excludes probands with hospital treatment)	5 (83.3%)	21 (100%)	N.S.
Hospitalization	1 (14.0%)	2 (9.0%)	N.S.

TABLE III. Demographic and clinical characteristics of probands with panic distorder and MDD probands by source of proband ascertainment

	ECA (n = 13)	Anxiety Clinic (n = 52)	Depression Clinic (n = 12)	p value
Sex				
Male	3 (29.1%)	9 (17.3%)	1 (8.3%)	N.S.
Female	10 (76.9%)	43 (82.7%)	11 (91.7%)	
Age (years)	44.6	42.8	39.8	N.S.
Mean (S.D.)	(11.1)	(8.8)	(5.9)	
Social class	2.92	3.03	2.66	N.S.
Mean (S.D.)	(0.95)	(0.96)	(0.48)	
Age of onset of panic (years)	27.8	28.4	27.1	N.S.
	(11.9)	(10.4)	(9.36)	
Mean (S.D.)				
Impairment (panic)	9 (69.2%)	7 (13.7%)	9 (75%)	0.0001
None/mild	4 (30.8%)	44 (86.3%)	3 (25%)	
Moderate/severe				
Impairment (MDD)	3 (23.1%)	10 (19.2%)	1 (8.3%)	N.S.
None/mild	10 (76.9%)	42 (80.8%)	11 (91.7%)	
Moderate/severe				
No. of panic symptoms during	5.54	3.38	6.92	0.0001
worst episode				
Mean (S.D.)	(2.67)	(2.58)	(2.50)	
Co-morbidity				
Social phobias	2 (15.4%)	9 (17.39%)	0	N.S.
Simple phobias	3 (23.1%)	19 (36.5%)	1 (8.3%)	N.S.
Alcohol abuse/dependence	3 (23.1%)	14 (26.9%)	4 (33.3%)	N.S.
Drug abuse dependence	0 (0.0%)	9 (17.3%)	2 (16.6%)	N.S.
Outpatient treatment (excludes probands			11 (100%)	N.S.
with hospital treatment)	11 (91.7%)	40 (100%)		
Hospitalization	1 (7.7%)	12 (23.1%)	1 (8.3%)	N.S.

TABLE IV. Sequence of onset of panic and MDD in probands with panic with MDD by source of proband ascertainment

Onset of panic and depression	ECA (n = 13)	Anxiety Clinic (n = 52)	Depression clinic (n = 12)	p value
Simultaneous onset	4 (30.8%)	16 (30.8%)	6 (50%)	N.S.
Primary panic	6 (46.1%)	17 (32.7%)	4 (33.3%)	
Primary depression	3 (23.1%)	19 (36.5%)	2 (16.7%)	

trists. However, a higher proportion of probands ascertained through the Anxiety Clinic tended to have moderate to severe impairment associated with their worst episode of panic disorder than probands ascertained through the ECA, although this difference was not significant. In addition a higher proportion of those probands ascertained through the ECA had co-morbid social and simple phobias although these differences were also not statistically significant.

Probands with panic disorder and major depression. There were no significant differences found in age, sex or social class by source of proband ascertainment in probands with major depression (Table III). The proportion of those probands with moderate or severe impairment as a result of their worst episode of panic disorder was significantly higher in probands ascertained through the Anxiety Clinic compared to probands ascertained through the ECA (Table III). Not surprisingly, probands ascertained through the depression clinic were significantly less impaired by their worst episode of panic disorder than those ascertained through the anxiety clinic. However, as with probands who had panic without depression, the number of panic symptoms during worst episode was greater in probands ascertained through the ECA than those ascertained

through the Anxiety Clinic; the number of panic symptoms during worst episode were also greater in probands ascertained through the Depression Clinic when compared to probands ascertained through the Anxiety Clinic. These findings suggest that there may be a qualitative difference in panic disorder among patients who seek treatment at an Anxiety Clinic compared to those seeking treatment at a Depression Clinic. Also of interest is the fact that probands ascertained through the Depression Clinic are less likely to have co-morbid social and simple phobias when compared to probands ascertained through either the ECA study or the Anxiety Clinic, although these differences did not reach statistical significance.

Sequence of onset of panic and MDD in probands. Because of the importance given to the primary/secondary distinction in onset of panic and major depression by clinicians, we investigated the sequence of onset of the two disorders by source of proband ascertainment. The sequence of onset of the two disorders in probands with both panic and major depression, by source of proband ascertainment is shown in Table IV. Probands were categorized into three mutually exclusive categories according to whether (a) the two disorders occurred simultaneously (simultaneous onset), (b) the first onset of panic occurred before the first onset of depression (primary panic) or (c) the first onset of depression occurred before the first onset of panic (primary depression). There is no statistically significant association between the sequence of onset of the two disorders and the source of proband ascertainment ($\chi^2 = 3.223$, d.f. = 4, p = 0.521). These results suggest that the chronological definition of primary/secondary panic is not the factor that differentiates panic probands treated at the Anxiety Clinic from those treated at the Depression Clinic.

Relative characteristics by source of proband ascertainment

There were no significant differences found in the distribution of age, sex or interview status among relatives in the two groups (Table V).

Rates of panic in relatives by source of proband ascertainment

There was no significant difference in rates of panic in relatives of probands with panic without depression by source of proband ascertainment (Table VI). Overall rates of panic (not differentiating between those with and without depression) were not significantly different in relatives of probands ascertained

through the ECA study when compared to relatives of probands ascertained through the anxiety clinic. Furthermore, neither the rates of "panic without depression" nor the rates of "panic with depression" in relatives were found to differ significantly in relatives of the two proband groups. These results must however be interpreted with caution because of the small number ($n = 7$) of probands ascertained through the ECA study.

Adjusted odds ratios, comparing the odds of developing panic in relatives of probands with panic without MDD ascertained through the Anxiety Clinic to the odds of developing panic in relatives of probands with pain without MDD, ascertained through the ECA are shown in the later half of Table VI. It will be noted that none of these odds ratios are significantly different from one, implying that there is no difference in these odds, even when controlling for the potential confounding effects of age, sex and interview status. These results indicate that there is no significant association between the rates in relatives and the source of proband ascertainment (i.e. Anxiety Clinic or ECA study) even when controlling for these potential confounding factors.

Results shown in Table VII indicate that for relatives of probands with panic and MDD, rates of panic in relatives of ECA probands are almost identical to rates of panic in relatives of probands from the Anxiety Clinic and adjusted odds ratios comparing these two groups, controlling for potential confounding factors, are not significantly different from one. However, rates of panic in relatives of probands ascertained through the Depression Clinic were lower than the rates in relatives of both ECA probands and of probands from the Anxiety Clinic, although the difference was not found to be statistically significant.

DISCUSSION

Our results can be summarized as follows.

Proband differences by source of ascertainment

(1) Probands with panic disorder with or without MDD ascertained through the ECA were less impaired than those probands ascertained through the Anxiety Clinic; these differences in the level of impairment were statistically significant only in the probands with panic and MDD. This finding supports the hypothesis that probands coming for treatment as compared to those selected from the general population are more severely ill with respect to the disorder for

TABLE V. Demographic characteristics of relatives by source of proband ascertainment

(a) *Probands with Panic without MDD*

Demographic characteristics of relatives	ECA (n = 33)	Anxiety Clinic (n = 108)	p value
Sex			N.S.
Male	19 (57.6%)	55 (50.9%)	
Female	14 (42.4%)	53 (49.1%)	
Age			N.S.
Mean (S.D.)	52.4 (19.6)	49.3 (18.1)	
Interview status			
Interviewed	15 (45%)	59 (55%)	N.S.
Non-interviewed	18 (55%)	49	

(b) *Probands with Panic with MDD*

	ECA (n = 73)	Anxiety Clinic (n = 304)	Depression Clinic (n = 65)	p value
Sex				N.S.
Male	33 (45%)	156 (51.5%)	35 (53.9%)	
Female	40 (55%)	148 (48.7%)	30 (46.2%)	
Age	46.4	48.2	46.4	N.S.
Mean (S.D.)	(18.5)	(18.3)	(18.5)	
Interview status				
Interviewed	30 (41%)	121 (40%)	28 (43%)	N.S.
Non-interviewed	43 (59%)	183 (60%)	37 (57%)	

TABLE VI. Rates of panic disorder in relatives of panic without depression probands by source of proband ascertainment

Disorder	ECA (n = 33)	Anxiety Clinic (n = 108)	p value
Panic	15.2% (5)	13.9% (15)	1.000
Panic without depression	6.1% (2)	8.3% (9)	0.956
Panic with depression	9.1% (3)	5.6% (6)	0.749

Adjusted*odds ratios comparing rates of panic in relatives of probands with panic without MDD ascertained through the Anxiety Clinic with relatives of probands with panic without MDD ascertained through the ECA study

Disorder in relatives	Odds ratio	p value
Panic	0.870	0.646
Panic without depression	1.11	0.8057
Panic with depression	0.711	0.397

*Adjusted for age, sex and interview status.

which they are being treated. Interestingly, we found that probands with panic with MDD ascertained through the Depression Clinic were less impaired by panic than similar probands ascertained through an Anxiety Clinic. However, there were no differences by source of proband in

degree of impairment associated with the worst episode of MDD.

(2) Probands ascertained from both the ECA and the Depression Clinic had more panic symptoms associated with their worst episode of panic than those probands ascertained through the Anxiety

TABLE VII. Rates of panic disorder in relatives of probands with panic with MDD by source of proband ascertainment

Disorder in relatives	ECA (n = 73)	Anxiety Clinic (n = 304)	Depression Clinic (n = 65)	p value
Panic	8.2% (6)	8.9% (27)	3.1% (2)	0.289
Panic without depression	0.0% (0)	3.9% (12)	3.1% (2)	0.23
Panic with depression	8.2% (6)	4.9% (15)	0.0 (0)	0.074

Adjusted* Odds ratios comparing rates of panic in relatives of clinic probands to ECA probands

Disorder: panic Contrast	Odds ratio	p value
Anxiety Clinic vs ECA	1.08	0.943
Depression Clinic vs ECA	0.61	0.232

*Adjusted for age, sex and interview status.

Clinic, despite the fact that probands from the Anxiety Clinic were more likely to have moderate to severe impairment.

(3) When co-morbidity with other relevant psychiatric disorders was examined we found that contrary to conventional wisdom, probands selected from the community through the ECA study had as much co-morbid simple and social phobia as well as co-morbid alcohol abuse/dependence as probands ascertained through the Anxiety Clinic. The only exception was the absence of co-morbid drug abuse/dependence in probands ascertained through the ECA. However, we found that probands ascertained through the Depression Clinic had no co-morbid social phobias and very little simple phobias compared to probands ascertained through the Anxiety Clinic as well as probands ascertained through the ECA.

Comparison of rates in relatives by source of proband ascertainment

Despite differences on some important clinical characteristics in probands by source of ascertainment, rates of panic disorder in relatives of probands who had panic without MDD, as well as in relatives of probands who had panic with MDD, did not differ significantly by source of proband ascertainment. Although these results must be interpreted with caution because of the small number of probands from the ECA and the Depression Clinic, it is somewhat reassuring to observe that when comparing relatives of ECA probands with relatives of probands from the Anxiety Clinic the rates themselves are very similar in the two groups for probands who had panic without depression (15.2% vs 13.9%), and are virtually identical (8.2% vs 8.9%) for relatives of probands who had panic with depression, in these

two groups. Thus, it is unlikely that the lack of statistically significant differences in the rates between the two groups is due to a lack of power because of small sample size. However, rates of panic in relatives of probands who had panic with depression and were ascertained from the depression clinic were lower (3.1%) than rates in relatives of probands in the other two groups (8.2%, 8.9%) although these differences were not found to be statistically significant.

Implications

Results of this study have the following implications for studies of familial aggregation of panic disorder.

(1) There is no evidence to suggest that selecting probands from treatment centers rather than from the community overestimates the rates of panic disorder in relatives.

(2) Contrary to conventional wisdom, there is little to suggest that patients selected from treatment centers are in general more likely to have co-morbid disorders than cases identified through a population survey.

(3) Rates of panic disorder in relatives of probands who had panic with depression and were selected from the depression clinic are consistent with previously published rates in 133 relatives of 22 probands with depression and panic disorder, which was found to be 3.8% (Leckman et al., 1983). Taken together these results seem to suggest that individuals who have panic with MDD, and seek treatment at an Anxiety Clinic, may differ from individuals who have panic with MDD, and seek treatment at a Depression Clinic, in terms of familial transmission of panic disorder. Despite the fact that this difference was not found to be statistically significant in the data presented in this paper, the findings seem to

suggest that relatives of probands with panic and MDD ascertained through a Depression Clinic tend to have lower rates of panic disorder than relatives of probands ascertained through an Anxiety Clinic. This could account for discrepancies found in the familial aggregation of panic disorder in previous studies where probands were selected from Anxiety Clinics as contrasted with Depression Clinics (Leckman et al., 1984). This result underscores once again our previous conclusion that panic disorder with MDD is a heterogenous disorder (Weissman et al., 1993).

Limitations

The major limitation of the study is that the number of probands ascertained through the community sample as well as the number of probands ascertained through the depression clinic who had panic without MDD was small. Thus, these results should be interpreted with caution. However it is reassuring to note that the rate of panic disorder is very similar in relatives of ECA probands and relatives of probands from the Anxiety Clinic, for panic probands both with and without MDD. Furthermore, rates in relatives of probands with panic disorder and MDD ascertained through the Depression Clinic had *lower* rates of panic disorder than relatives of ECA probands with panic disorder and MDD. These findings, taken together, indicate that it is unlikely that the lack of significant differences in rates between treated and untreated groups is primarily due to a lack of power because of small numbers of probands in some of these groups. Nevertheless, further investigations using larger samples are needed to confirm the findings that we have reported in this paper.

CONCLUSIONS

Our data do not support the hypothesis that familial aggregation of panic disorder in relatives of probands ascertained in treatment settings is greater than that in relatives of probands ascertained from the community. Further research is needed to determine if this finding applies to other psychiatric disorders as well.

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