

Panic Disorder History in the Families of Patients With Angiographically Normal Coronary Arteries

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Objective: The authors evaluated the diagnostic validity of an interview-based panic disorder diagnosis in cardiology chest pain patients with angiographically normal coronary arteries. **Method:** Patient probands with normal coronary arteries (N=65) were first contacted immediately after their normal angiogram and were given a structured diagnostic interview. On the basis of the results of the interview, probands were grouped as having panic disorder (N=19), panic attacks that did not meet frequency criteria for panic disorder (N=17), or no panic (N=29). At a later time, patient probands were recontacted and given a structured family-history interview that inquired about psychopathology in their first-degree biological relatives (N=544). **Results:** As predicted, panic disorder was significantly more prevalent among the first-degree relatives of probands with normal coronary arteries diagnosed with panic disorder or panic attacks than among the family members of probands with normal coronary arteries without panic (17.4% versus 15.7% versus 4.0%). Family members of probands with panic attacks were significantly more likely to be diagnosed with major depression than were the family members of probands with no panic; however, differences did not reach significance for family members of the panic disorder proband group. Groups did not differ significantly in familial alcoholism. **Conclusions:** These data support the construct validity of an interview-based panic disorder diagnosis among patients with chest pain and normal coronary arteries and suggest that these patients could benefit from treatment for panic disorder.

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Approximately one-third to one-half of cardiology patients with chest pain and normal coronary arteries meet diagnostic criteria for panic disorder (1, 2); however, several factors call into question the validity of an interview-based panic disorder diagnosis for these patients. Some researchers, for example, have maintained that the chest pain of patients with normal coronary arteries may best be explained by difficult to document cardiovascular abnormalities such as "microvascular angina" (3) or gastrointestinal abnormalities (4). Similarly, although some patients with normal coronary arteries technically meet the criteria for panic disorder, they demonstrate a demographic and symptom profile that is atypical for this diagnosis (5). These findings have led some researchers to suggest that the problems of patients with normal coronary arteries only mirror panic states (6). Thus, although many pa-

tients with normal coronary arteries do meet the criteria for an interview-based panic disorder diagnosis, additional corroborating evidence would appear to be necessary to support the validity of this diagnosis in patients with normal coronary arteries.

Assessment of familial patterns of mental disorder is commonly used to evaluate the validity of putative diagnostic entities (7). It is well documented that the risk for panic disorder in the first-degree relatives of psychiatric patients with panic disorder is two to five times higher than that in control samples (8, 9). Similarly, studies show that 56%-67% of panic disorder patients have at least one first-degree relative with panic disorder (8, 9); again, this is a much higher rate than that found in the general population.

If, as we maintain, panic disorder is a valid diagnosis in patients with chest pain and normal coronary arteries, we would predict a high risk for panic disorder in the first-degree relatives of patients who had normal coronary arteries and this diagnosis, but not in the relatives of other patients with normal coronary arteries. Furthermore, we would expect familial risk for panic disorder among patient probands with normal coronary arteries and a diagnosis of panic disorder to be compa-

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rable to that among probands with panic disorder identified in psychiatric samples (i.e., 15%–20%) (8, 9). For cardiology patients with normal coronary arteries who did not have a diagnosis of panic disorder, however, we would expect a familial rate of panic disorder that is comparable to that found in normal control subjects (3%–5%). Secondarily, because major depression and alcoholism commonly co-occur with panic disorder (8, 10, 11), we would also expect to find higher rates of these disorders in the relatives of patients with normal coronary arteries and with panic disorder than in the relatives of other patients with normal coronary arteries. The purpose of this study was to test these predictions.

METHOD

Subjects

For this study we attempted to recontact all 94 patients with normal coronary arteries and chest pain who were originally assessed by Beitman et al. (1) approximately 3 years before the present study period. At that time, patients were recruited through a university cardiology clinic immediately after cardiac catheterization. To participate in the original study, patients had to have less than 30% stenosis of all major epicardial arteries and no other cardiac abnormalities that could explain their chest pain. The 65 patients we were able to contact at the follow-up assessment served as proband informants for this study. The final proband group consisted of 20 women and 45 men with a mean age of 56.1 years (SD=11.2 years). Comparisons between participants (N=65) and nonparticipants (N= 29), using the original baseline data obtained by Beitman et al. (1), revealed no significant differences on diagnostic variables related to the current study.

Procedure

On the original contact (baseline), Beitman et al. (1) administered the Structured Clinical Interview for DSM-III (SCID) (12) to each patient. On recontact, approximately 3 years later (follow-up), we administered the Family Informant Schedule and Criteria adapted for *DSM-III-R* (13) to patient probands in order to assess panic disorder, major depression, and alcoholism in all biological, adult, first-degree relatives aged 18 or older, living or deceased, for whom there was adequate information (N=544). The Family Informant Schedule and Criteria is an extension of the Family History Research Diagnostic Criteria developed by Endicott et al. (14). The interview is designed to allow a clinician interviewer to systematically obtain diagnostic information on family members from a proband informant. Rules for coding diagnostic certainty include three categories: definite, probable, and possible. We assigned diagnoses to family members only if they were coded with a definite level of diagnostic certainty.

Using a graded set of techniques for locating study sub-

jects for follow-up, outlined by Russell Noyes (personal communication, March 1989), we attempted to recontact all 94 patients assessed by Beitman et al. (1) during the baseline phase. Sixty-five patients (69%) gave informed consent and served as proband informants. Of the remaining 29 patients, we were unable to locate 19, nine refused to participate, and one was deceased.

On telephone contact, we attempted to set up an appointment for patients to come to our clinic (N=21) to be interviewed; if this was not possible, we attempted to arrange to interview the patient over the telephone (N=44). The interviewer (M.G.K.) was blind to patients' baseline diagnoses. Patients were paid for their participation.

Study Groups and Dependent Variables

For all study analyses, the probands and their first-degree relatives were grouped on the basis of proband baseline SCID diagnosis. Three groups were formed: panic disorder probands, who met all *DSM-III* criteria for panic disorder; panic attack probands, who experienced panic attacks but not at the frequency required for a diagnosis of panic disorder; and probands with no panic, who did not experience panic attacks. There were two dependent variables of interest in this study: the percentage of first-degree relatives of probands with a study diagnosis (panic disorder, major depression, alcoholism) and the percentage of probands with at least one first-degree relative with a study diagnosis.

RESULTS

Table 1 shows sample characteristics of probands and their first-degree relatives for the three proband groups. Statistical comparisons were accomplished by using analysis of variance for continuously distributed variables and chi-square tests of association for dichotomous variables. The only significant group difference for these variables was the age of study probands. As shown, the probands with panic disorder were significantly younger than probands with no panic; the age of probands with panic attacks was intermediate and not significantly different from the other two proband groups (Tukey's multiple comparison test, $\alpha=0.05$).

Group comparisons on the percentage of probands' first-degree relatives with panic disorder confirmed study predictions. The overall 2 (familial panic disorder diagnosed versus not diagnosed) \times 3 (panic attack versus panic disorder versus no panic disorder proband group membership) chi-square analysis was significant ($\chi^2=18.58$, $df=2$, $N=544$, $p<0.01$). As shown in figure 1, the panic disorder and panic attack proband relative groups did not differ significantly in the percent of members diagnosed with panic disorder (17.4%, $N=29$ of 167 relatives, versus 15.7%, $N=22$ of 140 relatives, respectively). However, both of these relative groups had significantly more members diagnosed with panic disorder than was true for the group made up of the

TABLE 1. Characteristics of Probands With Chest Pain and Normal Coronary Arteries and of First-Degree Relatives, by Proband's Panic Attack Status

Group and Item	Proband Group		
	Panic Disorder	Panic Attack	No Panic
Probands			
Number	19	17	29
Gender			
Male			
Number	14	12	19
Percent	73.7	70.6	65.5
Female			
Number	5	5	10
Percent	26.3	29.4	34.5
Age (years) ^a			
Mean	51.2	54.7	60.2
SD	11.3	10.6	11.4
First-degree relatives			
Number	167	140	237
Members per family			
Mean	8.8	8.2	8.2
SD	4.3	3.7	3.4
Gender			
Male			
Number	86	71	123
Percent	51.5	50.7	51.9
Female			
Number	81	69	114
Percent	48.5	49.3	48.1
Age (years)			
Mean	49.5	50.5	54.3
SD	7.4	10.7	8.7

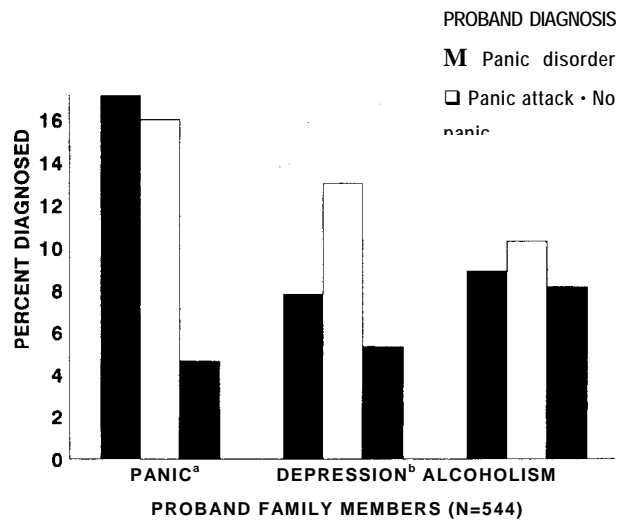
^aSignificant group difference ($F=3.93$, $df=2$, 64 , $p<0.05$).

relatives of the no panic disorder probands (4.0%, $N=11$ of 237 relatives).

Figure 1 also shows proband group differences in the percentage of first-degree relatives diagnosed with major depression. As predicted, the chi-square test confirmed that there was a significant overall effect for group membership ($\chi^2=6.67$, $df=2$, $N=544$, $p<0.05$). Again, as predicted, follow-up tests showed that probands with panic attacks had a higher percentage of first-degree relatives with major depression than did probands with no panic (12.9%, $N=18$, versus 5.5%, $N=13$; figure 1). However, failing to confirm study predictions, probands with panic disorder did not differ significantly from either of the other two proband groups on this variable. Finally, and again failing to confirm study predictions, proband groups were highly similar in the extent to which alcoholism was diagnosed for first-degree relatives (figure 1).

Table 2 shows proband group comparisons of the percentage of probands having at least one first-degree relative with panic disorder, major depression, and alcoholism. As shown, the overall group comparisons for panic disorder were significant. Compared to probands with no panic, significantly more probands with panic disorder and probands with panic attacks had at least one first-degree relative with panic disorder ($\chi^2=8.53$, $df=1$, $N=48$, $p<0.01$; $\chi^2=4.60$, $df=1$, $N=46$, $p<0.05$, respectively). Again, the panic attack and panic disorder

FIGURE 1. DSM-III Diagnoses in First-Degree Relatives of Probands With Chest Pain and Normal Coronary Arteries, by Proband's Panic Attack Status



^aSignificant difference between family members in the panic disorder proband group and those in the no panic proband group ($\chi^2=15.72$, $df=1$, $N=404$, $p<0.01$) and between family members in the panic attack proband group and those in the no panic proband group ($\chi^2=10.70$, $df=1$, $N=377$, $p<0.01$).

^bSignificant difference between family members in the panic attack proband group and those in the no panic proband group ($\chi^2=6.47$, $df=1$, $N=377$, $p<0.01$).

proband groups did not differ significantly on this variable. Thus, the pattern of group differences in the percentage of probands with any panic disordered relatives confirms study predictions and parallels group comparisons of the total percentage of family members diagnosed with panic disorder reported earlier.

Table 2 also shows that, compared to the no panic group, the panic attack group, but not the panic disorder group, had a higher percentage of probands with at least one relative diagnosed with major depression. Table 2 shows that the overall test of this effect approached statistical significance. Exploring the source of this statistical trend further, we again found that only differences between the panic attack and the no panic proband groups were significant ($\chi^2=4.50$, $df=1$, $N=46$, $p<0.05$). Thus, study predictions for this variable were confirmed for the panic attack group but not for the panic disorder proband group. Finally, and again consistent with the negative findings for alcoholism noted earlier, table 2 shows that we found virtually no group difference in the percentage of probands with at least one first-degree relative diagnosed with alcoholism.

DISCUSSION

Study findings support the validity of an interview-based panic disorder diagnosis among patients with

TABLE 2. Probands With Chest Pain and Normal Coronary Arteries Who Had Relatives With *DSM-III* Diagnoses, by Proband's Panic Attack Status

Relative's <i>DSM-III</i> Diagnosis	Proband Group					
	Panic Disorder (N=19)		Panic Attack (N=17)		No Panic (N=29)	
	N	%	N	%	N	%
Panic disorder ^a	12	63.2	9	52.9	6	20.7
Major Depression	6	31.6	10	58.8	8	27.6
Alcoholism	8	42.1	7	41.2	12	41.4

^aSignificant group effect ($\chi^2=9.76$, $df=2$, $N=65$, $p<0.01$).

^bNearly significant effect ($\chi^2=4.82$, $df=2$, $N=65$, $p<0.10$).

normal coronary arteries. As predicted, the percentage of first-degree relatives diagnosed with panic disorder was significantly higher for probands who themselves received an interview-based diagnosis of panic disorder (17.4%) or panic attack (15.7%) than for the relatives of probands not diagnosed with panic (4.0%). Similarly, we found that 63.2% of the probands with panic disorder and 52.9% of the probands with panic attacks had at least one first-degree relative with a panic disorder diagnosis; however, this was true for only 20.7% of the probands with no panic.

As predicted, these group differences correspond with past studies that compared familial psychopathology in psychiatric samples of panic disorder probands with that of normal control subjects (8, 9). This outcome would not have been expected, however, if panic symptoms in patients with normal coronary arteries only mirrored panic states, as has been suggested by some writers (3, 4, 6). Specifically, we were able to make largely accurate a priori predictions both about the direction and magnitude of group differences in familial panic disorder. If a condition other than panic disorder were actually the source of symptoms in patients with panic disorder and patients with panic attacks, there would be no reason to expect the specific group differences that we predicted and found. Therefore, the conclusion that panic disorder identified in patients with normal coronary arteries and their families is the same syndromal entity as panic disorder identified in psychiatric samples would appear to be the most parsimonious interpretation of these findings.

Findings associated with major depression and alcoholism, however, were somewhat less straightforward. Although these findings were partially supportive of study predictions, it is unclear why the family members of probands with panic attacks, but not of probands with panic disorder, showed higher levels of major depression than relatives of probands with no panic. Our failure to find group differences in familial rates of alcoholism may reflect earlier findings suggesting that alcohol-related problems are uncommon among patients with normal coronary arteries and panic disorder (1). In addition, at least one family study reports that while risk for alcoholism is higher among the family members

of agoraphobic patients with panic attacks, this is not the case for the relatives of probands with uncomplicated panic disorder (15). These findings may have implications for those of the present study, as Beitman et al. (1) reported very low levels of agoraphobic avoidance among the patients with panic and normal coronary arteries who were used as subjects in this study.

Several methodological features may limit the generalizability of these findings. First, there can be little question that our use of proband informants to gain diagnostic information about family members (family history method) will yield generally less accurate results than would have the direct interviewing of the family members themselves (family study method). For example, several studies that directly compared these two methods report that the family history method significantly underreports familial psychopathology (16, 17). On the basis of these findings, we could expect that the degree of familial psychopathology in all of our study groups was actually higher than that reported here. Nevertheless, because there is no reason to believe that such a bias should operate differentially among the proband groups, our study conclusions would appear to remain unaffected.

A second issue that may be relevant to the generalizability of these findings is the relative reliability of the telephone interview (68% of the study cohort) versus the personal interview (32% of the cohort) method used in data collection. Although few studies have directly compared these two methods, Colombotos (18) reported that both yielded similar results in a systematic question-and-answer format unrelated to psychiatry. More recently, Paulsen et al. (19) found that diagnoses of panic disorder, depression, and alcohol abuse (the same diagnoses assessed in the current study) could reliably be obtained by using a telephone interview. Using a 12- to 19-month test-retest design, Paulsen et al. reported kappa values ranging from 0.69 to 0.84. Because these values are comparable to, or greater than, those obtained for these diagnoses by using personal interviews (20), it would appear to be likely that the reliability of our data collection methods was adequate.

In addition to the previous interpretational caveats, there could have been an undetected interaction between proband informant diagnosis and response bias to family interview questions. For example, probands who experience panic attacks themselves could be more sensitized to panic symptoms in their relatives and hence more likely to report such symptoms. However, this interpretation appears to be inconsistent with past findings, noted earlier, which show that the family history method tends to underreport rather than overreport familial psychopathology. Beyond this observation, however, it is clear that the appropriate way of ruling out this potential interpretational confound is a replication of this study in which family members are interviewed directly.

Finally, although we do document hypothesized differences in the familial rate of panic disorder for probands with normal coronary arteries who themselves

either do or do not experience panic attacks, this study was not designed to assess the causes of these group differences. That is, although we argue that the pattern of study findings supports the validity of the panic disorder diagnosis among patients with normal coronary arteries, addressing the nature of the mechanisms by which panic disorder is transmitted to family members is well beyond the scope of this study. For example, because panic has been shown to have a genetic component (21), it may have been that the panic attack and panic disorder groups (but not the no panic group) were likely to share a panic-related genetic vulnerability with their biological family members. Alternatively, environmental factors affecting the likelihood of a diagnosis of panic may have been more common in the panic attack and panic disorder groups. Almost assuredly, some combination of these two explanations is more appropriate than is either alone.

In conclusion, these findings corroborate an increasing body of research showing that chest pain for which no medical cause can be firmly identified may be associated with panic disorder (22). Past studies have documented that the symptoms of many cardiology patients with undiagnosed chest pain meet descriptive diagnostic criteria for panic disorder (1, 2). Supporting the view that these are bona fide cases, the current study shows that panic disorder is common in the families of patients with panic and normal coronary arteries but not in the families of other patients with normal coronary arteries. Because effective treatments for panic disorder are available (8), it will be important that patients with normal coronary arteries are routinely evaluated for panic disorder and, when appropriate, referred for treatment.

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