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Validating Studies for Panic Disorder in Patients with Angiographically Normal Coronary Arteries

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Patients with angiographically normal coronary arteries have a low risk of cardiac death and a low risk for nonfatal myocardial infarction. To a person with severe chest pain, the absence of coronary artery disease should be reassuring. Nonetheless, a significant percentage of these patients continue to have chest pain[28] that interferes with normal work and social functioning.[31, 35, 44, 45]

When no physical explanation for continuing chest pain is found, a psychosomatic explanation should be considered. Psychological treatment for atypical noncardiac chest pain has been shown to be effective.[32] In some cases, this may even extend to actual diagnosis of a psychiatric illness. If a specific diagnosis can be given, therapeutic strategies may be more easily defined.

Patients with chest pain and normal coronary arteries have certain characteristics that make panic disorder a possible explanation for their chest pain. First, they score high on measures of hypochondriasis,[36] a finding also reported in panic disorder patients.[42] Secondly, earlier studies showed that they often met the criteria for anxiety neurosis, which preceded panic disorder in early versions of the DSM.[6] Thus, we hypothesized that panic disorder is associated with chest pain in normal coronary arteries.

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APPLYING A MODEL FOR ESTABLISHING THE VALIDITY OF PSYCHIATRIC DIAGNOSES

Chart reviews for panic attack symptoms[38] and psychiatric interviews[14] in patients with chest pain and normal coronary arteries appeared to support our original hypothesis. However, a simple description of a clinical phenomenon is an inadequate index of diagnostic validity. Feighner et al[24] have described five phases for establishing the validity of psychiatric diagnoses: clinical description, laboratory studies, follow-up studies, family studies, and delineation from other disorders. In this article, we show how we used these criteria to assess the validity of our interview finding that patients with chest pain and normal coronary arteries have a high rate of panic disorder.

CLINICAL DESCRIPTION

A preliminary requirement for demonstrating diagnostic validity is clinical description of the observed phenomenon; that is, what are the features observed clinically, and which features are commonly observed together? For our purposes, this step included the following: (1) determining the base rate of panic disorder in the population of persons with chest pain and normal coronary arteries, and (2) given a finding that panic disorder occurs at a high rate, establishing that other disorders that commonly co-occur with panic disorder also occur in this population.

Panic Disorder in Patients with Angiographically Normal Coronary Arteries

As already noted, in one early study 37% of patients with normal or near-normal coronary arteries had anxiety neurosis.[6] We[38] subsequently hypothesized that a significant percentage of patients with angiographically normal coronary arteries would be likely to have panic attack symptoms. By retrospectively examining the charts of 123 patients with angiographically normal coronary arteries, we found that 40% of this group described attacks of four or more panic symptoms (including chest pain). Concurrently, a study at another location found that 12 of 28 patients (43%) with normal coronary arteries fit the DSM-III[1] criteria for panic disorder.[29]

In our next study,[14] we sought to test the hypothesis that a significant number of patients with angiographically normal coronary arteries have panic disorder using a larger, prospective sample. Patients with chest pain undergoing cardiac catheterization at the University of Missouri Hospital were considered for the study if they were found to have normal coronary arteries. Patients with any coronary lesion causing 30% or more stenosis were excluded from the study.* Also excluded were patients with any other possible physical cause of chest pain, including mitral valve prolapse.

*Although stenosis of 50% or below is generally considered "normal" or "hemodynamically insignificant," patients with 30% to 50% stenosis generally show more coronary events and higher cardiac mortality than those with 0% to 30% stenosis.[46] Therefore, 30% or less stenosis is a more conservative definition of hemodynamically insignificant occlusion.

The 94 patients who consented to participate (37 men and 57 women) ranged in age from 24 to 78 years, with a mean of 50.1 years. The patients were interviewed, and the questionnaires were administered in the evening of the catheterization or during the next morning.

The Structured Clinical Interview for DSM-III-Upjohn version (SCID-UP)[49] was administered to subjects by clinical psychiatrists trained in its use. To receive a diagnosis of panic disorder, the subject had to meet DSM-III-R[2] criteria for panic disorder and had to have had at least one panic attack per week for the past 3 weeks. This frequency criterion is more conservative than the DSM-III-R and increases the likelihood that the patient is in need of treatment because of the ongoing, repetitive nature of the attacks. Panic attacks were defined as "discrete periods of discomfort or fear" accompanied by at least four of the symptoms listed in Table 1. During at least some of the attacks, most of the symptoms needed to be experienced within 10 minutes of the beginning of the first symptom. The SCID-UP[49] also provided for the diagnoses of social and simple phobia and current and past episodes of major depression and substance abuse. This was important because all of these disorders can co-occur with panic disorder.

Thirty-two of the 94 subjects (34%) fit the criteria for panic disorder. None reported a social phobia, and 10 reported at least one simple phobia. Twenty-three of the 94 (22%) reported a lifetime prevalence of at least one major depressive episode. Eleven of the subjects (12%) had a current major depressive episode, and 9 of the 11 had simultaneous panic disorder (the relationship between panic disorder and depression in this population will be described more fully in the next section).

In comparing the panic versus no-panic groups, there were no differences in sex (60% female in both groups), but the panic group was significantly younger (mean age of 45 versus 53). The panic disorder group scored significantly higher on several self-report measures including the Beck Depression Inventory[5] (14 versus 8) and the Zung Anxiety Scale[57] (52 versus 44).

Table 1. *Panic Attack Symptoms*

Periods of intense fear or discomfort accompanied by at least four of the following symptoms:
1. Shortness of breath
2. Choking or smothering sensations
3. Palpitations or tachycardia
4. Chest pain or discomfort
5. Sweating
6. Faintness
7. Dizziness
8. Nausea or abdominal distress
9. Depersonalization or derealization
10. Numbness or tingling (paresthesias)
11. Flushes or chills
12. Trembling or shaking
13. Fear of dying
14. Fear of going crazy or doing something uncontrolled

Concurrent Diagnoses

The validity of our interview findings would be further substantiated if diagnoses that often co-occur with panic disorder in the general psychiatric population are also found in the normal coronary artery and chest pain population. Common psychiatric diagnoses associated with panic disorder include depression, agoraphobia, and substance abuse.[5, 15, 35] On the other hand, the cardiology population may have unique characteristics that increase or decrease the likelihood of these concurrent diagnoses. As mentioned, in our original sample of 94 persons undergoing cardiac catheterization, we not only assessed for panic disorder, but also for depression, agoraphobia, and alcohol use.

Depression. Panic disorder and major depression have much in common, most importantly that each responds favorably to similar classes of psychiatric medications.[18] Furthermore, the two disorders often co-occur, and it appears that persons with both disorders do not respond as well to treatment as persons with only one.[27, 34] Researchers have determined the lifetime prevalence of major depression in persons with panic disorder to be greater than 40% in most samples.[16, 17, 21, 39, 43] A similar prevalence of depression was found in a cardiology outpatient sample by Beitman et al,[9] who found that 19 of 43 (44%) cardiology outpatients experiencing atypical or nonanginal chest pain and panic disorder also had a lifetime history of major depression.

In the previously described sample of 94 patients with angiographically normal coronary arteries, 12 of the 32 (37.5%) who had panic disorder also had a lifetime history of major depression, and 9 of these 12 were having a current major depressive episode at the time of the interview. Panic disorder patients with a history of major depression also were more impaired on a number of measures than panic disorder patients without a history of major depression. They reported more panic symptoms in their most recent panic attack, reported more symptomatology on the Brief Symptom Inventory[22] (both total score and seven of nine subscales), and had higher scores on the Zung Self-Rating Anxiety Scale[57] and Beck Depression Inventory.[8] Thus, we concluded that panic disorder is linked to major depression in the cardiology patient population, just as it is in the psychiatric patient population, and that chest pain patients with concurrent major depression and panic disorder may be more debilitated than those with panic disorder alone.[15] This further demonstrates the validity of an interview-based panic disorder diagnosis in chest pain patients with angiographically normal coronary arteries.

Agoraphobia. Most researchers have found a strong association between agoraphobia and panic disorder; reported rates of agoraphobia in panic disorder patients range from 40% to 92%.[16, 42, 51, 52] However, in a general outpatient cardiology sample of persons who had atypical or nonanginal chest pain, we found that only 8 of 43 patients who met criteria for panic disorder also had agoraphobia.[8] Although this was a heterogenous sample, the finding raises questions about the close association between panic disorder and agoraphobia, at least in the cardiology populations.

In our more homogeneous sample of 94 patients undergoing cardiac catheterization, only 2 (6%) of the 32 patients who met criteria for panic

disorder also reported some phobic avoidance. This suggests that in cardiology settings, unlike psychiatric settings, agoraphobia is not often found with panic disorder.

Patient self-selection may explain why cardiology populations have a lower rate of agoraphobia than do psychiatric populations.[15] When Epidemiological Catchment Area data,[35] psychiatric data, and cardiology data are considered together, it appears that people with both panic attacks and agoraphobia seek psychiatric help, whereas people with panic disorder alone seek help from internists and general practitioners, who may refer them to cardiologists when they have chest pain. Symptom patterns in panic disorder patients with and without agoraphobia lend support to this idea. Noyes et al[41] found that panic disorder patients with agoraphobia have somatic symptoms localized in the head or psychological symptoms of panic, whereas those without agoraphobia report more general somatic symptoms. Furthermore, Ganellen et al[25] found that panic disorder patients with agoraphobia are more likely to endorse items of cognitive distortion. Both these findings suggest that patients with panic disorder and agoraphobia experience their illness as a psychiatric one, whereas patients with panic disorder alone interpret their symptoms as somatic. If this is true, one would expect to find relatively few patients with panic disorder and agoraphobia in a cardiology setting.

Substance Abuse. Alcohol problems and anxiety disorders have high co-morbidity, and alcohol use in these patients may represent an attempt to self-medicate the anxiety symptoms, because anxiety symptoms precede alcohol use in most samples. In inpatient alcohol treatment settings, agoraphobia occurs in up to 45% of the patients. However, the relationship between panic disorder uncomplicated by agoraphobia and alcohol abuse seems much less definite. Kushner et al[34] hypothesize that the unremitting fears associated with agoraphobia may serve as a strong motivation to drink, compared to panic disorder, which is characterized by acute, time-limited attacks.

Given that there were relatively few agoraphobics in our sample of patients with angiographically normal coronary arteries, we expected to find few patients with panic disorder who abused alcohol. This was indeed the case; only 3 of 32 (9%) had a history of alcohol abuse, none of whom met criteria for panic disorder with agoraphobia.

Summary

We found that approximately one third of a sample of 94 patients with chest pain and angiographically normal coronary arteries meet the diagnostic criteria for panic disorder. Furthermore, like psychiatric panic disorder samples, they had a high rate of concurrent depression. Unlike psychiatric samples, however, agoraphobia and alcohol abuse were relatively uncommon, but this may be due to patient self-selection. Our findings provide support for our hypothesis that panic attacks may explain some occurrences of chest pain in this population. Further steps to validate the panic disorder diagnosis are described in the next section.

LABORATORY CHALLENGE STUDIES

Carbon Dioxide Challenge Tests

Laboratory studies (e.g., chemical, physiologic, radiologic, and anatomic), when consistent with a defined clinical description, provide additional validating data. Because 35% carbon dioxide has been shown to trigger panic attacks in patients with panic disorder,[53] and this response reliably discriminates between panic disorder patients and other anxiety disorder patients,[26] we hypothesized that normal coronary artery patients with panic disorder would respond with anxiety symptoms to carbon dioxide challenge, whereas those without panic disorder would not.[13]

The subjects included 11 persons who had a recent normal or near-normal cardiac catheterization, 6 of whom had panic disorder and 5 of whom did not, and a control group of 10 persons who had neither a history of cardiac catheterization nor panic disorder. Normal coronary patients were recruited via their cardiologists, and controls were recruited via newspaper advertisements.

Before the carbon dioxide procedure, all subjects were interviewed using the SCID-UP-R[50] to assess for panic disorder, major depression, and substance abuse. They also completed the Zung Anxiety Scale,[57] Brief Symptom Inventory (BSI),[22] and Chronic Panic Inventory.

Three sets of double inhalations were performed: practice with mask disconnected from gases, room air, and 35% carbon dioxide. Data on acute anxiety symptoms were gathered before and after each inhalation using the Acute Panic Inventory, a 28-item symptom checklist. Ten minutes were allotted between inhalation sets, and subjects were blind to ordering of gases inhaled.

The three subject groups did not differ significantly in sex, age, and history of major depression or substance abuse. At baseline, patients with normal coronary arteries and panic disorder scored significantly higher on the Chronic Panic Inventory and approached significantly higher scores on the Zung Anxiety Scale[57] and baseline Acute Panic Inventory than either normal coronary patients without panic disorder or normal controls. The two groups of normal coronary artery patients approached having significantly higher total Brief Symptom Inventory scores than the control group (subscales were not used).

The results of the carbon dioxide procedure were as follows: The normal coronary artery patients with panic disorder became significantly more anxious, as measured by the Acute Panic Inventory, than the other two (non-panic disorder) groups after inhaling carbon dioxide, compared to baseline ($P = 0.03$). They also showed a marginally higher difference in Acute Panic Inventory anxiety ratings after inhaling carbon dioxide compared to after inhaling room air ($P = 0.09$). These results indicate that the normal coronary artery panic disorder group was more likely to respond to carbon dioxide challenge with acute anxiety symptoms than the other two groups (those not receiving the panic disorder diagnosis).

Note that the 35% carbon dioxide challenge is a highly sensitive but not very specific test for panic disorder.[53] In our study, two control subjects had a significant symptom response to 35% carbon dioxide, and two patients

with normal coronary arteries and panic disorder did not respond to carbon dioxide with increased panic symptoms (one of these nonresponders had a recent history of panic disorder but did not meet the diagnostic criteria at the time of the study). These discrepancies are consistent with previous 35% carbon dioxide challenge studies.[53]

In spite of its small sample size, this study suggests that compared to normal controls and patients with normal coronary arteries but without panic disorder, patients with normal coronary arteries and panic disorder respond to 35% carbon dioxide with a statistically significant increase in panic symptoms. This finding supports interview results showing that panic disorder exists and is prevalent in patients with angiographically normal coronary arteries.

Lactate Challenge Test

An additional laboratory study further corroborates the interview-based panic disorder diagnosis in patients with normal coronary arteries and chest pain. The sodium lactate challenge test is also commonly used as a diagnostic marker for panic disorder, although its merits are disputed.[20, 36] Recently, Russell et al[48] gave this challenge test to 31 patients with angiographically normal coronary arteries and non-fear panic disorder. Atypical chest pain and other panic symptoms resulted in 87% of them. Non-fear panic disorder is a variant of panic disorder in which the fear symptoms are absent (i.e., the patient does not report fear of doing something uncontrolled, going crazy, or dying while having a panic attack); it has been shown to occur in patients with angiographically normal coronary arteries.[12]

FOLLOW-UP STUDIES

According to Feighner et al,[24] the purpose of follow-up studies in establishing the validity of a psychiatric diagnosis is to determine if a cause other than the proposed diagnosis can be found for long-term outcome. Specifically, although the originally diagnosed illness may be variable over time, patients with this diagnosis should have similar outcomes, compared to patients without the diagnosis. With regard to our own work with chest pain patients with normal coronary arteries, the long-term outcome for those who have panic disorder should be distinguishable from those who do not.

Functioning at Follow-Up

Although mortality risk in patients with normal coronary arteries is low, these patients still are at significant risk for long-term disability.[28, 35, 44-46] At least one study suggested to us that panic disorder marks normal coronary artery patients for long-term disability.[7] Therefore, we sought to confirm this hypothesis in our sample of chest pain patients with angiographically normal coronary arteries. We did this by carrying out a follow-up study of psychiatric diagnosis, functional status, and self-perceived illness in these patients.

We obtained follow-up data from 72 of the 94 original patients via a

combination of in-person and telephone interviews and self-report questionnaires. Subjects were divided into two groups based on whether or not they had panic disorder at the original assessment or at follow-up, or both. The follow-up assessment, which took place an average of 38 months later, included several self-report measures of disability, medical and mental services used since catheterization, and the Brief Symptom Inventory,[22] Zung Self-Rating Anxiety Scale,[57] and Marks-Mathews Fear Inventory.[37] In addition, subjects were assessed for current or past (since catheterization) panic disorder, major depression, and substance use using the Structured Clinical Interview for DSM III-R, Upjohn version (SCID-UP-R).[30]

As in previous studies, the sample experienced continuing disability but no mortality. As hypothesized, however, the patients who had panic disorder were significantly more impaired at follow-up than those who did not have panic disorder. They reported more debilitating chest pain, viewed themselves as more disabled, reported more major depressive episodes and alcohol abuse, and had lower exertional capacity. Panic disorder patients also had higher anxiety levels and general psychological distress, as measured by the Zung and Brief Symptom Inventory questionnaires, respectively, and were less functional socially. There was a statistical trend for them to be more likely to be taking cardiac medications. On the other hand, they were not more likely to be unemployed or to have sought medical treatment (this is probably due to a ceiling effect because nearly all of the sample, regardless of panic status, had done so). Also, they did not report having more fears.[11]

Change in Diagnosis

Based on preliminary analyses, it appears that patients with panic disorder at the original assessment were for the most part continuing to have panic attacks at the second assessment, although they did not always meet panic disorder criteria. Several patients had also developed agoraphobia between assessments, signifying worsening psychiatric condition. On the other hand, patients who did not have panic disorder at the original assessment were highly unlikely to develop it in the interim. It thus seems likely that the problems that normal coronary artery patients with panic disorder were experiencing at the original assessment were not due to another disorder, and although the course of their panic disorder varied over time, it rarely remitted completely. This is in agreement with previous studies of panic disorder, which have characterized it as a serious, chronic disorder if left untreated.[3, 40, 52]

FAMILY STUDIES

Assessing familial patterns of mental disorder is a common method used to evaluate the validity of putative diagnostic entities. It is well documented that the risk for panic disorder in the first-degree relatives of probands with panic disorder (15% to 20%) is two to five times higher than in control samples.[5] Thus, to the extent that panic disorder is a valid diagnosis in patients with chest pain and angiographically normal coronary

arteries, it would be expected that the risk for panic disorder would be similarly elevated in the first-degree relatives of normal coronary artery patients with an interview diagnosis of panic disorder but not in the family members of other patients with normal coronary arteries.[33]

Using the same sample described in the section on follow-up studies, subjects served as proband informants and provided responses to a structured family interview covering all of their biologic adult first-degree relatives for whom there was adequate information (n = 544). Based upon the results of a structured diagnostic interview (SCID-UP-R)[50] of the probands, we formed two groups: those probands with a lifetime history that included panic disorder ("PD proband"; n = 33), and those without a lifetime history of panic disorder ("No PD proband"; n = 32). All family history interviews were conducted with the interviewer blind to proband diagnosis.

The major study prediction was confirmed by the finding that panic disorder is significantly more common in relatives of probands with panic disorder and normal coronary arteries than in the relatives of other normal coronary artery patients. Family members of PD probands were over four times more likely to be diagnosed with PD than were those of No PD probands. Furthermore, 48.5% of the PD probands had at least one family member with panic disorder, as compared to only 9.4% of the No PD probands. Family members of PD probands were also more likely than others to be diagnosed with depression (10.7% versus 4.1%).

The two groups were similar on both proband and family member demographic characteristics, except that the PD probands were younger and had younger family members than the No PD probands (mean proband age of 51.76 versus 60.63; mean family member age of 49.00 versus 54.88). Notably, these findings indicate that those in the No PD proband group were actually exposed to a longer morbidity risk period, increasing their probability of receiving a diagnosis. Inasmuch as this element of the study design works against the confirmation of the study hypotheses, confidence in the robustness of these results is further buttressed.

DELIMITATION FROM OTHER DISORDERS

Because different disorders can have similar clinical features, it is necessary to exclude from studies those patients with other disorders that may explain their symptoms, as well as any doubtful or borderline cases. In order to support our hypothesis that a sizable percentage of chest pain patients with normal coronary arteries have panic disorder, other diagnoses, both psychiatric and physical, must be ruled out. The DSM-III-R[2] specifically states that panic disorder symptoms must not be due to a known physiologic cause.

In all our studies, rigorous criteria have been applied to screen out doubtful cases from both medical and psychiatric standpoints. Our main group of 94 patients had to have 30% or less stenosis, so coronary artery disease could not explain the extent of their symptoms. Patients whose history suggested a physical cause for their chest pain were also excluded.

Similarly, they had to meet diagnostic criteria *more* stringent than those in the DSM-III[1] in order to be considered panic disorder patients.

Other psychiatric disorders, such as somatization disorder, personality disorders, and other anxiety disorders are possible alternate diagnoses. Although we have not assessed these possibilities, several observations seem relevant. First, the symptoms of panic disorder, unlike the alternate disorders, occur in "spells" or attacks, and we believe that the SCID-UP and SCID-UP-R[49, 50] reliably discriminate between acute phenomena such as panic attacks and more chronic ones such as generalized anxiety disorder. Second, and perhaps more importantly, any of the preceding disorders can and do occur simultaneously with panic disorder,[47] so even if another diagnosis can be made, the panic disorder diagnosis may still be a valid one. Finally, panic disorder can be effectively treated by both pharmacologic[4] and cognitive-behavioral[5] therapies. There is preliminary evidence that panic disorder symptoms in patients with normal coronary arteries are responsive to standard antipanic treatment.[14]

Several physical disorders have also been implicated in chest pain with normal coronary arteries. Among these are microvascular angina[19] and a variety of esophageal disorders,[30] which are discussed elsewhere in this issue. Our results suggest that patients with panic disorder represent a *subset* of normal coronary artery patients; the remainder may have these or other diagnoses. However, the overlap among these disorders has not been studied, and all three are relatively new diagnostic entities. Clearly, future studies in this area will have to use more stringent exclusion criteria in order to obtain a sample of patients whose chest pain is definitely associated with panic disorder.

CONCLUSIONS

In this article, we have reviewed evidence relevant to the diagnostic validity of panic disorder in patients with chest pain and angiographically normal coronary arteries. We have used five criteria to establish the validity of our hypothesized diagnosis of panic disorder in a sample of 94 patients. Our findings should reduce skepticism among those mental health professionals and medical colleagues who have raised doubts about the existence of panic disorder in this population.

Our findings provide logical grounds for the hypothesis that panic is etiologically associated with disability over time in normal coronary artery patients. Edlund and Swann[23] report that the direct and indirect costs of long-term disability due to panic disorder can be tens of thousands of dollars per patient, not to mention the high social costs of the disorder. The additional medical care sought by normal coronary artery patients with panic disorder probably pushes these costs even higher.

However, one major validity study remains: Do patients with angiographically normal coronary arteries and panic disorder respond to known antipanic treatments? An uncontrolled, open-label trial of alprazolam in 20 patients with chest pain, panic disorder, and no evidence of coronary artery disease showed a modest treatment response.[10] A double-blind medication

study involving Richter and Bradley at the University of Alabama and Wulsin at the University of Cincinnati is currently underway to study the efficacy of clonazepam in these patients. If this study shows that they respond favorably, then all physicians seeing patients with chest pain and normal coronary arteries should consider panic disorder in the differential diagnosis.

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