CLINICAL CHARACTERISTICS OF FAMILIAL GENERALIZED ANXIETY DISORDER

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The authors seek to determine whether the clinical characteristics of generalized anxiety disorder (GAD) differ in individuals with a high vs. low familial vulnerability to illness. We identified 486 personally interviewed female twins from a population-based register who had both an interviewed co-twin and a lifetime history of GAD using modified DSM-III-R criteria which required a one-month minimum duration of illness. We attempted to predict risk for GAD in the co-twin from the clinical features of the GAD in the proband twin using the Cox proportional hazard model, controlling for year of birth and zygosity. Only two variables uniquely predicted an increased risk for GAD in the co-twin: number of GAD symptoms endorsed and comorbidity with bulimia. Variables that did not uniquely predict risk of illness in the co-twin included age at onset, duration of the longest episode and number of episodes. The familial vulnerability to GAD can be meaningfully indexed by clinical features of the syndrome. These results suggest that if the syndrome of GAD is to be narrowed, it would, from a familial perspective, be more valid to increase the minimum number of required symptoms rather than to increase the minimum duration of illness. Anxiety 1:186–191 (1994/1995). © 1995 Wiley-Liss, Inc.

INTRODUCTION

Although generalized anxiety disorder (GAD) was formally proposed as a diagnostic category less than 20 years ago (Spitzer et al., 1975; Brown et al., 1994), the criteria for this disorder have, during this period, been revised many times. The minimum duration of illness has variously been set at two weeks (Spitzer et al., 1975), one month (American Psychiatric Association, 1980) or six months (American Psychiatric Association, 1987). The minimum number of required symptoms has varied from one out of five (Spitzer et al., 1975), at least one from three of four groups (American Psychiatric Association, 1980), six out of eighteen (American Psychiatric Association, 1987) and most recently, to three out of six (American Psychiatric Association, 1994). Various diagnostic hierarchies have also been applied to GAD, ranging from excluding GAD syndromes when they are "due to" another mental disorder (American Psychiatric Association, 1980) or excluding cases which meet criteria only during episodes of psychotic or mood disorders (American Psychiatric Association, 1987, 1994) or only when also meeting criteria for a psychotic dis-order, a mood disorder, Briquet's syndrome or panic disorder (Spitzer et al., 1975).

Although concern has been expressed about the validity of GAD as a diagnostic category (Barlow et al., 1986; Breslau et al., 1987; Breier et al., 1985; Brown et al., 1994), few studies have explicitly attempted to validate diagnostic criteria for this disorder. Breslau and Davis (1985), for example, found that a six-month minimum duration of illness may more confound than improve the descriptive validity of GAD.

Familial aggregation remains one of the most important validating criteria for psychiatric disorders (Robins and Guze, 1970). In this report, we examine results from a population-based study of female twins to determine the clinical characteristics of GAD that predict familial aggregation.

METHODS

SAMPLE

Characteristics of this sample have been outlined previously (Kendler et al., 1992a). In brief, this sample of Caucasian female same-sex twins, born from 1934 to 1971, was obtained from the population-based Virginia Twin Registry, formed from a systematic review of birth records in the Commonwealth of Virginia from 1915 onward. Twins were eligible to participate if both members of the pair responded to a mailed questionnaire, the response rate to which was approximately 64%. Of the 2,352 individuals from 1,176 twin pairs who met these criteria, we succeeded in personally interviewing 2,163 (92.0%) of them, including both members of 1,033 pairs. Of the completed interviews, 89.3% were performed face to face and 10.7% by telephone. No difference was found in the rate of GAD in those assessed by these two methods. The mean age (± S.D.) of the sample at interview was 30.1 ± 7.6. Zygosity was determined by the use of standard self-report questions, photographs, and when uncertain, genotyping by DNA polymorphisms. Final zygosity diagnoses yielded 590 MZ, 440 DZ and 3 pairs of unknown zygosity.

MEASURES, INTERVIEWERS AND DIAGNOSTIC REVIEW

A lifetime diagnosis of GAD was made using an adaptation of an early version of the Structured Clinical Interview for DSM-III-R Diagnosis (SCID; Spitzer et al., 1987), a reliable instrument for the diagnosis of GAD (Riskind et al., 1987). This adaptation differed from current versions of the SCID in three significant ways. First, the introductory question was modified to inquire about periods of at least *one* rather than *six* months in duration. Second, no question inquired whether the anxiety or worry affected two or more life circumstances. Third, the SCID item inquiring about one of the 18 symptomatic criteria for GAD (#11, "flushes or chills") was inadvertently left off the interview, reducing the total number of symptomatic criteria from 18 to 17.

The lifetime diagnosis of GAD was based on a blind review by K.S.K., an experienced psychiatric diagnostician, using DSM-III-R criteria (American Psychiatric Association, 1987), except that the required minimum duration of illness was reduced from six months to one month and issues of diagnostic hierarchy were ignored. GAD was not diagnosed when the symptoms were considered due to medical illness or medication. In addition, lifetime diagnoses were made using DSM-III-R criteria for panic disorder, major depression, al-

cohol dependence, anorexia nervosa and bulimia nervosa. With two exceptions, we applied, for these diagnostic categories, unmodified DSM-III-R criteria. For bulimia, we included "subsyndromal" bulimic-like syndromes because in this sample they closely resembled, from both an epidemiologic and a genetic perspective, those cases meeting full DSM-III-R criteria (Kendler et al., 1991). Phobia was defined as the presence of one or more irrational fears that objectively interfered in the respondent's life. Based on the approach used by Leckman et al. (1983) in a study of major depression, probands with GAD with a lifetime diagnosis of major depression or panic disorder are divided into those where the disorders were always associated with GAD episodes (here termed *contemporaneous* comorbid cases) and those that were, at least some of the time, separate from the GAD episodes (here termed *non-contemporaneous* comorbid cases).

All interviewers, who underwent extensive and ongoing training during the field study, had a minimum of either a Master's degree in Psychology or Social Work or a Bachelor's degree and at least two years clinical experience. The same interviewer never interviewed both members of a twin pair.

If a twin answered positively to the "stem" question for GAD on the SCID, and answered positively to at least five of the symptomatic criteria, then she was asked three additional questions about her episodes of GAD including: (1) age at first episode, (2) total number of episodes, and (3) length of longest episode.

Inter-rater reliability was assessed in 53 jointly conducted interviews. Each of these interviews was blindly reviewed and the percent agreement and chance corrected agreement (Cohen, 1960) for the diagnosis of GAD was 91% and + 0.77 ± 0.10 ($p < 0.001$), respectively.

TREATMENT OF INDIVIDUAL SYMPTOMS

While it would be of interest to determine the relationship between each individual symptom and risk for GAD in the co-twin, the performance of 17 separate tests would introduce an unacceptably high probability of a spurious positive finding. Therefore, for the purpose of data reduction, we submitted a product-moment correlation matrix for all 17 symptoms to a factor analysis and VARIMAX rotation (SAS Institute, 1985; results available on request). Three factors were identified and (along with the items with the heaviest loading, all positive), in descending order, were as follows: **autonomic hyperactivity** (shortness of breath, palpitations, dizziness, feeling shaky and sweating), **hypervigilance** (trouble concentrating, trouble sleeping, exaggerated startle, irritability, muscle tension and keyed up) and **gastrointestinal symptoms** (dry mouth, frequent urination, restlessness, upset stomach and lump in throat). "Easy fatigability" did not load distinctly on any three of these factors. Similar factors were obtained if the factor analysis was conducted using tetrachoric correlations. Factor scores for these three factors were used in subsequent analyses.

STATISTICAL ANALYSIS

Since our goal was to examine the relationship between clinical characteristics of GAD in affected twins and the risk for GAD in their co-twins, our analysis focused on pairs of observations: a proband twin with GAD and her co-twin. Twin pairs where neither had a lifetime diagnosis of GAD were, per force, excluded from the analysis. The remaining pairs could be divided into two groups: (1) pairs where only one twin had GAD, which are "counted" once in our analysis, and (2) pairs where both twins had GAD, which are "counted" twice in our analysis.

Since GAD has an age-dependent onset and our sample is variable with respect to age, we utilized the Cox proportional hazard model, as operationalized in the PHGLM procedure in SAS (SAS Institute, 1986). In the Cox model, the dependent variable is the hazard rate for GAD, defined as the risk for a previously unaffected twin to develop GAD in a given unit of time, here a year. A twin with no lifetime diagnosis of GAD is retained in the analysis until her current age, at which point she is "censored" (i.e., removed) from the analysis.

Although "double" counting twins from concordant pairs does not result in a bias in parameter estimation (McGue et al., 1984), some correction is required for incorrectly assuming the independence of the observations from these doubly counted twin pairs (n = 83). If T is the total number of observations, N the number of doubly counted twin pairs, and P the number of parameters in our model, we multiplied the standard errors obtained by $[(T-P)/(T-N-P)]^{1/2}$. Although approximate, this correction is likely to be conservative (Kish and Frankel, 1974). All significances reported are based on our corrected standard errors. In the stepwise proportional hazard model, we used entry and exit criteria of 0.50 and 0.10, respectively. For all analyses, we utilized the traditional $p \leq .05$ criterion for significance. All χ^2 analyses from the Cox analyses have one degree of freedom.

We wanted in all our analyses to control for two variables: zygosity and year of birth. Zygosity was included to control for the higher risk observed in MZ vs. DZ co-twins of affected twins (Kendler et al., 1992a). Year of birth was included to control for any possible cohort effect for GAD. Probandwise concordance, tetrachoric correlations and biometrical model fitting for GAD in this sample have been reported previously (Kendler et al., 1992b).

RESULTS

CHARACTERISTICS OF THE SAMPLE

Clinical Features. Key clinical characteristics of the 486 twins with GAD, who had a mean age (± S.D.) at interview of 28.7 ± 9.0, are seen in Table 1. This sample had a mean and median number of episodes of 4.2 and 2, respectively. The mean and median dura-

TABLE 1. Clinical features of GAD in the proband twin that predict risk for GAD in the co-twin[a]

Variable	Mean ± S.D.	χ^2	p
Age at onset	22.5 ± 8.5	0.00	0.957
Number of symptomatic criteria	9.3 ± 2.9	18.58	0.000
Maximum duration (weeks)	29.4 ± 78.9	0.02	0.886
Number of episodes	4.2 ± 9.8	5.20	0.022

[a]Controlling for zygosity and year of birth.

tion of the longest episode of illness was 29.4 and 9 weeks, respectively. The mean and median number of total endorsed symptoms was 9.3 and 9, respectively.

Comorbidity. The proportion of twins meeting criteria for GAD who also made criteria for a lifetime diagnosis of the other assessed psychiatric disorders is seen in Table 2 and ranged from 1.6% for anorexia nervosa to 48.5% for phobia. The proportion of twins with GAD who met criteria for major depression and panic disorder *only* during episodes of GAD was 23.7 and 3.3%, respectively.

PREDICTION OF RISK FOR GAD IN THE CO-TWIN: VARIABLES TAKEN ONE AT A TIME

Clinical Features. The relationship between the clinical characteristics of GAD in the proband and the risk for GAD in the co-twin, as assessed by the Cox Proportional Hazard model, controlling for zygosity and year of birth, is presented in Table 1. Both the number of endorsed symptomatic criteria and the total number of episodes significantly predicted an increased risk for GAD in the co-twin (p = 0.000 and 0.022, respectively). However, neither age at onset of GAD nor maximum duration of an episode bore any relationship to the risk for GAD in the co-twin.

Comorbidity. The impact of comorbidity, taken one disorder at a time, on the risk for GAD in the co-twin is seen in Table 2. While the co-occurrence in the proband twin of any disorder increased the risk for

TABLE 2. Comorbidity as a predictor of risk for GAD in the co-twin[a]

Disorder	Kind	Frequency (%)	χ^2	p
Major depression	NC[b]	45.1	0.19	.662
Major depression	C[b]	23.7	0.64	.423
Panic disorder	NC	13.0	4.89	.029
Panic disorder	C	3.3	0.31	.576
Phobia	LT[b]	48.5	0.87	.351
Alcohol dependence	LT	12.8	1.82	.177
Bulimia	LT	9.7	4.28	.039
Anorexia	LT	1.6	0.09	.760

[a]Controlling for zygosity and year of birth.
[b]NC, noncontemporaneous; C, contemporaneous; LT, lifetime.

GAD in the co-twin, this effect was statistically significant only for non-contemporaneous panic disorder and bulimia (p = 0.029 and 0.039, respectively).

Symptoms. Controlling for zygosity and year of birth, **autonomic hyperactivity** (χ^2 = 4.66, p = 0.031), and **hypervigilance** (χ^2 = 9.72, p = 0.002) significantly and positively related to the risk of GAD in the co-twin, while the results for **gastrointestinal symptoms** were nearly significant (χ^2 = 3.54, p = 0.060). Since total number of endorsed symptoms was strongly related to risk for GAD in the co-twin, we repeated the analysis of the symptom factors, controlling for the total number of endorsed symptoms. In these analyses, none of the symptom factors any longer significantly predicted risk of GAD in the co-twin: **autonomic hyperactivity** (χ^2 = 1.09, p = 0.297), **hypervigilance** (χ^2 = 1.00, p = 0.317) and **gastrointestinal symptoms** (χ^2 = 0.01, p = 0.939).

PREDICTION OF RISK FOR GAD IN THE CO-TWIN: MULTIVARIATE ANALYSIS

Finally, we conducted a stepwise proportional hazards regression that began with all the variables previously considered. Only two variables uniquely predicted the risk of GAD in the co-twin: total number of symptoms (χ^2 = 18.60, p = 0.000) and comorbidity with bulimia nervosa (χ^2 = 4.33, p = 0.038). (The third variable entered into the stepwise regression, total number of episodes, was accepted into the model but then rejected because its p value, 0.184, exceeded 0.10.) Doing a median split, the relative risk for GAD in the co-twin of proband twins with ≤ 9 vs. > 9 endorsed symptoms was 1.72. The relative risk tended to increase if the threshold for number of symptoms increased: ≤ 10 vs. > 10 – 1.68, ≤ 12 vs. > 12 – 1.89, ≤ 14 vs. > 14 – 2.52 and ≤ 16 vs. > 16 – 5.46. The relative risk for GAD in the cotwins of proband twins with versus without a diagnosis of bulimia nervosa was 1.69.

DISCUSSION

We found that it was possible to relate clinical and etiologic heterogeneity in GAD. Individuals with a high familial vulnerability to GAD, as reflected by the risk for GAD in their co-twins, systematically differed in certain of their clinical characteristics from twins with a low familial vulnerability.

The strongest unique predictor of risk of illness in relatives was the number of endorsed symptoms. In GAD, an individual's familial vulnerability to illness is apparently indexed by the number of symptoms experienced and reported. These results are in striking contrast to a parallel analysis in this same data set of major depression (Kendler et al., 1994) in which the number of endorsed symptoms was unrelated to the risk for depression in the co-twin. Unlike with major depression, our findings suggest that the validity of the GAD syndrome, from a familial perspective, might

be increased if a larger number of symptoms were required to meet diagnostic criteria.

The other unique predictor of risk for GAD in relatives was lifetime comorbidity with bulimia. The same result occurred in our parallel analysis of major depression in this sample (Kendler et al., 1994), suggesting that bulimia in women may reflect a high familial vulnerability to several inter-related psychiatric syndromes.

Length of longest episode of GAD was unrelated to the risk for GAD in the co-twin. From a familial perspective, a longer minimum duration of GAD does not appear to increase the validity of the diagnostic category. These results do not support the substantial prolongation of the minimal duration of a GAD episode from one month in DSM-III to six months in DSM-III-R and DSM-IV.

Number of episodes significantly predicted the risk for GAD in the co-twin, but when other factors were controlled for, this result lost significance. These results suggest that recurrence in GAD is not as good an index of familial vulnerability to this illness as it is for major depression (Gershon et al., 1986; Bland et al., 1986; Kendler et al., 1994).

We were unable to find evidence that GAD presenting largely with somatic versus psychic symptoms (Hoehn-Saric et al., 1989) differed in familial vulnerability. Controlling for the total number of endorsed symptoms, the number of **hypervigilant** vs. **autonomic hyperactivity** items endorsed did not significantly relate to the risk for GAD in the co-twin. It may still be possible that in pairs of concordant twins, members resemble one another in their GAD symptom profiles. This question will be addressed in subsequent analyses.

Age at onset of GAD also was unrelated to the risk of illness in the co-twin. Early age at onset has been associated with increased familial vulnerability to illness for several neuropsychiatric disorders including Alzheimer's disease (Heston et al., 1981), alcoholism (Goodwin, 1984) and, in most studies, affective illness (Weissman et al., 1984). If our finding is confirmed, it suggests that age at onset of GAD may be influenced primarily by non-familial factors, which could include environmental stressors.

When using a one-month minimum duration of illness, GAD is quite a common disorder in the general population (Breslau and Davis, 1985; Wells et al., 1989; Robins and Regier, 1991; Kendler et al., 1992b). If the goal is to produce a GAD syndrome that is less common, our results suggest that, from a familial perspective, it will be more valid to increase the minimum number of required symptoms than to increase the required duration beyond the one month proposed in DSM-III.

LIMITATIONS

Our results should be interpreted in the context of three potential limitations. First, our results are relevant only for females. Although little is known about

gender differences in the familial influences on GAD, given the known differences in prevalence of anxiety disorder in men and women (Robins and Regier, 1991; Wells et al., 1989), it is possible that the familial vulnerability to GAD may manifest differently across sexes.

Second, as outlined above, the diagnostic criteria for GAD assessed in this study included most, but not all, of those included in the final version of DSM-III-R (American Psychiatric Association, 1987), the most significant change being a reduction in the minimum duration of illness from six to one month. We did not attempt analyses with "6-month" GAD, because of previous experience in this data set that this disorder was too rare to provide stable statistical estimates (Kendler et al., 1992b).

Third, in this report, we related the clinical characteristics of GAD to the tendency for GAD to *aggregate* in families. We have previously shown in this sample that the familial aggregation of GAD can be best explained as a result solely of genetic factors (Kahn et al., 1986). Therefore, the indices of familial GAD found in this report probably reflect the *genetic*, and not just the *familial*, liability to GAD. While it would have been desirable to demonstrate this directly, the class of analyses reported here cannot currently be performed with the more appropriate sophisticated methods, in large part because of the problems of multi-dimensional integration (Neale et al., 1989; Kendler et al., 1994). A more definitive resolution of the issues addressed in this report must await the availability of such models.

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