Generalized Anxiety Disorder in Women

A Population-Based Twin Study

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Little is known about the role of familial and genetic factors in the etiology of generalized anxiety disorder (GAD), a new disorder first proposed in DSM-III. We examine this question in 1033 female-female twin pairs from a population-based registry. Both members in each twin pair were “blindly” assessed by structured psychiatric interview. Our results suggest the following: (1) GAD is a moderately familial disorder; (2) the tendency for GAD to run in families seems to be due largely or entirely to genetic factors shared between relatives rather than to the effects of the familial environment; (3) the heritability of GAD, estimated at around 30%, is modest, with the remainder of the variance in liability resulting from environmental factors not shared by adult twins; (4) the heritability of GAD cannot be explained solely by the occurrence of GAD only during episodes of major depression or panic disorder; and (5) the etiologic role of genetic factors is probably similar in GAD with a 1- vs a 6-month minimum duration of illness.

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A major change in the nosology of the anxiety disorders appeared in DSM-III when the diagnostic category of anxiety neurosis, as articulated in DSM-II, was split into panic disorder, distinguished by paroxysmal episodes of intense anxiety, and generalized anxiety disorder (GAD), characterized by sustained “free-floating” anxiety. Since the publication of DSM-III, panic disorder has been accepted rapidly as a valid psychiatric disorder that has high reliability, aggregates in families, and has a distinct pattern of response to treatment. By contrast, GAD has remained more controversial and its validity has been questioned.

Symptomatic of the uncertainty regarding GAD has been the controversies over its duration and its place in the diagnostic hierarchy. In DSM-III, the minimum duration of GAD was set at 1 month. Without strong empirical support, this was increased in DSM-III-R to 6 months. It remains unclear whether this change has confounded or improved the validity of GAD. In DSM-III, GAD could not be diagnosed when it was “due to another mental disorder.” The hierarchy rules were narrowed in DSM-III-R where GAD cannot be diagnosed when it occurs only during the course of a mood or psychotic disorder.

Familial aggregation is an accepted validating criterion for psychiatric disorders. Although there are numerous family and twin studies of “anxiety neurosis,” we know of only four that have examined a GAD-like syndrome. Cloninger et al. in a “blind” family study, found no excess of anxiety disorder in relatives of probands with a GAD-like syndrome termed “other anxiety neurosis.” Noyes et al. in a nonblind family history study, found significantly higher rates of GAD in relatives of probands with GAD vs controls. Torgersen, in a sample of twins from Norway treated for psychiatric illness, found a concordance rate for GAD of 0% (0/12) in monzygotic (MZ) twins and 5% (1/20) in dizygotic (DZ) twins. Andrews et al. in a preliminary report from a volunteer sample of Australian twins, found no significant difference in concordance rates for DSM-III-defined GAD in MZ vs DZ twins.

In this report, we examine the etiologic role of genetic and environmental factors in GAD as assessed at personal interview in a large sample of female twins from the Virginia Twin Registry. We examine whether these results change with the use of a 1- vs 6-month minimum duration of illness or of different diagnostic hierarchies.

PATIENTS AND METHODS

The sample and our approach to the analysis of population-based twin data have been detailed elsewhere. Briefly, female-female twin pairs from the population-based Virginia Twin Registry were personally interviewed by social workers blind to the status of the cotwin. Zygosity was determined blindly by standard questions, photographs, and, when necessary, DNA. Ninety-two percent of eligible twins were successfully interviewed, 89% in person and 11% by telephone.

The diagnosis of GAD was made using an adaptation of an early version of the Structured Clinical Interview for DSM-III-R Diagnosis, which has been shown to diagnose GAD with high reliability. The introductory question was modified as follows: "Thinking back over your entire life, have you ever had a time for..."
status of cotwin) was included in these analyses as an index of a "cooperation effect." The impact of environmental similarity in childhood or adulthood was assessed by logistic regression employing a "dummy" dependent variable coded zero if both twins were concordant for affection status and one if they were discordant.

RESULTS

Lifetime Prevalence

Of the 2163 personally interviewed twins, 509 (23.5%) met criteria for GAD with a 1-month minimum duration of illness ("1-month GAD") diagnosed without hierarchies at some point in their lives. Eliminating subjects who met criteria for 1-month GAD only when they also met criteria for panic disorder or depression reduced the prevalence estimates to 22.5% and 16.7%, respectively.

Of the interviewed twins, 127 (5.9%) met criteria for lifetime GAD with a 6-month minimum duration of illness ("6-month GAD") diagnosed without hierarchies. This figure declined to 5.7% and 3.6% if subjects meeting criteria only during episodes of panic disorder and major depression, respectively, were eliminated.

Testing for Biases

We will, in this section, examine biases using the criteria of 1-month GAD diagnosed without hierarchies, as the large sample size gives us maximal power. In our sample, the probability of a lifetime diagnosis of 1-month GAD diagnosis is strongly and positively related to age at interview ($\chi^2 = 37.80$, $df = 1$, $P < .0001$). Controlling for the effect of age at interview, the risk of illness was unrelated to the method of interview (face to face vs telephone) or interview status of the cotwin (interviewed vs refused). However, zygosity was significantly related to risk for 1-month GAD ($\chi^2 = 5.33$, $df = 1$, $P = .02$), with DZ twins having higher rates than MZ twins. Of note, with 6-month GAD, a trend was observed in the same direction, but it fell far short of significance ($\chi^2 = 1.90$, $df = 1$, $P$ not significant). Controlling for the effect of age and zygosity, similarity with respect to the diagnosis of GAD in twin pairs was unrelated to environmental similarity either in childhood or in adulthood.

Probandwise Concordance

The population lifetime prevalence and probandwise concordance for the various definitions of GAD in MZ and DZ twins are seen in Table 1. With common disorders, a substantial degree of familial aggregation is consistent with a modest risk ratio in relatives vs the general population.

For 1-month GAD without hierarchies, the relative risks in MZ and DZ cotwins of affected twins were 1.8 and 1.2 times, respectively, those found in the general population. As predicted by the multifactorial threshold model, given constant heritability, the relative risk for GAD in cotwins vs the general population increases as the definitions become narrower and the disorder becomes rarer.

Twin Correlations

The tetrachoric correlations for the various definitions of GAD in MZ and DZ twins are seen in Table 2. For 1-month GAD diagnosed without hierarchies, the correlations in MZ and DZ twins were +.35 and +.12, respectively. Using a diagnostic hierarchy in which either panic disorder or major depression was placed above GAD produced modest declines in the MZ and DZ twin correlations that were not statistically significant.

With 6-month GAD, the lower prevalence rate produced much less difference between the two groups. For 6-month GAD diagnosed without hierarchy, the MZ and DZ twin correlations were virtually the same. By contrast, when panic disorder was placed above 6-month GAD in a diagnostic hierarchy, the MZ twin correlation substantially exceeded that found in DZ twins (+.29 vs +.13, respectively). When major depression was placed above GAD in the hierarchy, the MZ twin correlation, while low, had a very large SE (+.09±.22), being based on a single discordant pair.

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Table 1.—Lifetime Prevalence and Probandwise Concordance in MZ and DZ Twins for Various Definitions of GAD

<table>
<thead>
<tr>
<th>Minimum Duration, mo</th>
<th>Diagnoses Above GAD in Hierarchy†</th>
<th>Lifetime Prevalence of GAD</th>
<th>Probandwise Concordance for GAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZ</td>
<td>DZ</td>
<td>MZ</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>21.2</td>
</tr>
<tr>
<td>1 Panic disorder</td>
<td>20.1</td>
<td>24.4</td>
<td>20.1</td>
</tr>
<tr>
<td>1 Major depression</td>
<td>15.0</td>
<td>18.3</td>
<td>18.3</td>
</tr>
<tr>
<td></td>
<td>4.6</td>
<td>5.9</td>
<td>5.9</td>
</tr>
<tr>
<td>1 Panic disorder</td>
<td>4.5</td>
<td>5.6</td>
<td>4.5</td>
</tr>
<tr>
<td>1 Major depression</td>
<td>3.1</td>
<td>3.1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

†MZ indicates monozygotic; DZ, dizygotic; and GAD, generalized anxiety disorder.
‡The GAD would not be diagnosed when an individual met criteria only during episodes of panic disorder or major depression.
§Corrected, by regression analysis, for small mean differences in age in MZ and DZ twins.
¶A very unstable estimate as based on only a single concordant pair.

Table 2.—Correlations in Twins for Various Definitions of GAD

<table>
<thead>
<tr>
<th>Minimum Duration, mo</th>
<th>Diagnoses Above GAD in Hierarchy†</th>
<th>Tetrachoric Correlations ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZ</td>
<td>DZ</td>
</tr>
<tr>
<td>1</td>
<td>+.35 ± .07</td>
<td>+.12 ± .08</td>
</tr>
<tr>
<td>1 Panic disorder</td>
<td>+.35 ± .07</td>
<td>+.09 ± .09</td>
</tr>
<tr>
<td>1 Major depression</td>
<td>+.31 ± .08</td>
<td>-.06 ± .10</td>
</tr>
<tr>
<td></td>
<td>+.28 ± .15</td>
<td>+.28 ± .14</td>
</tr>
<tr>
<td>1 Panic disorder</td>
<td>+.29 ± .15</td>
<td>+.13 ± .16</td>
</tr>
<tr>
<td>1 Major depression</td>
<td>+.09 ± .22</td>
<td>-.30 ± .19</td>
</tr>
<tr>
<td>Threshold</td>
<td>+.34 ± .07</td>
<td>+.13 ± .08</td>
</tr>
<tr>
<td>Threshold</td>
<td>+.35 ± .07</td>
<td>+.08 ± .08</td>
</tr>
<tr>
<td>Threshold</td>
<td>+.27 ± .08</td>
<td>-.05 ± .10</td>
</tr>
</tbody>
</table>

†GAD indicates generalized anxiety disorder; MZ, monozygotic; and DZ, dizygotic.
‡The GAD would not be diagnosed when an individual met criteria only during episodes of panic disorder or major depression.

Multiple Threshold Model

One way to evaluate whether the differences in results obtained with the 1-month vs 6-month minimum duration of illness for GAD are meaningful or the result of random fluctuations is to fit multiple threshold models to these data. These models test whether the data obtained can be explained by a single continuum of liability to GAD with three categories: unaffected, affected with duration of more than 1 but less than 6 months, and affected with duration of 6 months or greater. Of the six models tested (two zygosities x three definitions of illness), only one failed at the 5% level, a result not different from chance expectation. For example, for GAD without hierarchies, the multiple threshold model fit very well for both MZ twins ($\chi^2 = 0.27$, $df = 5$, $P = $ not significant) and DZ twins ($\chi^2 = 2.16$, $df = 3$, $P = $ not significant).

Twin Model Fitting

The results of model fitting to the twin correlations for the various definitions of GAD are seen in Table 3. Because age at interview strongly predicts risk for GAD, the effect of age was incorporated into these models. For 1-month GAD diagnosed without hierarchies, the ACE and ADE models fit well (with $\chi^2$ goodness-of-fit values of 0.69 and 0.11, respectively). The CE model, however, did not fit as well and fit considerably worse than the ACE model ($\chi^2 = 3.67$, $P = .055$). By contrast, the AE model fit as well as the more complex models ($\chi^2 = 0.69$) and, because it contained one less parameter, was preferable. This model predicted that 30% of the liability to 1-month GAD diagnosed without hierarchies resulted from additive genetic effects, 67% resulted from individual-specific environment, and 3% resulted from the effect of age at interview.

The AE model, with qualitatively similar results, was also the preferred model for five other definitions of GAD: 1-month and 6-month GAD with panic disorder above GAD in a hierarchy and all three threshold models. For one definition of GAD (1-month GAD with major depression above GAD in the hierarchy), ADE was the preferred genetic model with $\alpha$ estimated at zero and $\beta^2$ as accounting for 27% of the variance in liability. Because of the high negative correlation between estimates of $a$ and $d$ in the ADE model, it is not possible with our sample size to separate the effects of additive and dominance genetic variance meaningfully. For the 6-month GAD diagnosed without hierarchy or with major depression above GAD in the hierarchy, the CE model provides the best fit. For all the 6-month definitions of illness, the differences between the goodness of fit of the models were quite modest.

COMMENT

We sought, in this report, to examine the etiologic role of genetic and environmental factors in GAD and to determine whether their roles differed when the minimum duration of GAD was varied or when different diagnostic hierarchies were applied. We will examine our major results in turn.

The Role of Genetic Factors in the Etiology of GAD

Contrary to the results of the two previous twin studies, we found evidence for the role of genetic factors in the etiology of GAD. Of the nine definitions of GAD tested, the best fitting model suggested that twin resemblance resulted solely from genetic factors in seven of them. These results, consistent with one but not the other previous family study of GAD, suggests that familial factors play a significant role in the etiology of this syndrome.

Estimates for the heritability of liability to GAD were modest, ranging from 19% to 30% for various definitions. These findings suggest that genetic factors play a significant, but not overwhelming, role in the etiology of GAD. For GAD, our results suggest that individual-specific environmental experiences will often play a critical role in determining who will become affected.

Comorbidity and GAD

Among twins who met criteria for a lifetime diagnosis of 1-month GAD, 4.3% of them had the disorder only while also meeting criteria for panic disorder and 28.9% of them had the disorder only while also meeting criteria for major depression. These results are similar to those found in the Epidemiologic Catchment Area study where 31.9% of cases of DSM-III GAD in women concurrently met criteria for either panic or major depression. Since their familial and genetic factors are probably important.
Table 3.—Results of Twin Model Fitting, Including Age, for Various Definitions of GAD*

<table>
<thead>
<tr>
<th>Minimum Duration, mo</th>
<th>Diagnoses Above GAD in Hierarchy</th>
<th>Fit of Model (in χ² Units)</th>
<th>Parameter Estimates of Best-Fitting Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ACE+ df=3 CE df=4 AE df=4</td>
<td>a²  d²  c²  e² Age²</td>
</tr>
<tr>
<td>1</td>
<td>...</td>
<td>0.69 4.36 0.69+</td>
<td>0.30 0.27 0.72 0.03</td>
</tr>
<tr>
<td>1</td>
<td>Panic disorder</td>
<td>1.22 5.39 1.22+</td>
<td>0.29 0.23 0.72 0.05</td>
</tr>
<tr>
<td>6</td>
<td>Major depression</td>
<td>4.82 6.63 4.82+</td>
<td>0.00 0.23 0.72 0.05</td>
</tr>
<tr>
<td>6</td>
<td>...</td>
<td>0.82 1.29 0.82+</td>
<td>... 0.23 0.72 0.05</td>
</tr>
<tr>
<td>6</td>
<td>Panic disorder</td>
<td>0.90 1.38 0.90+</td>
<td>0.23 0.20 0.72 0.01</td>
</tr>
<tr>
<td>6</td>
<td>Major depression</td>
<td>4.39 5.15 5.15+</td>
<td>... 0.20 0.72 0.01</td>
</tr>
<tr>
<td>Threshold</td>
<td>...</td>
<td>0.61 4.18 0.61+</td>
<td>0.28 0.20 0.68 0.04</td>
</tr>
<tr>
<td>Threshold</td>
<td>Panic disorder</td>
<td>1.87 6.70 1.87+</td>
<td>0.28 0.20 0.69 0.03</td>
</tr>
<tr>
<td>Threshold</td>
<td>Major depression</td>
<td>4.65 7.60 4.65+</td>
<td>0.19 0.20 0.80 0.01</td>
</tr>
</tbody>
</table>

*aGAD indicates generalized anxiety disorder.
†There are eight distinct observed statistics: the twin correlations of liability to depression in monoyzygotic (MZ) and dizygotic (DZ) twins, the regression of age onto this liability in twin 1 and twin 2 in the MZ and DZ pairs, the variance of age, and the variance of liability to depression. For the ACE model, we estimate five parameters: a, c, e, the regression of age onto the liability to depression, and the variance of age. Thus, this model has 8-5=3 degrees of freedom.
‡Best-fit model by information criterion of Akaike.

in the etiology of panic disorder and major depression, the role of genetic factors in the etiology of GAD could be merely an epiphenomenon of the comorbidity between GAD and these disorders. Our results, however, do not support this hypothesis. When subjects with GAD that occurred only when the individual also met criteria for panic disorder or major depression were excluded from the analysis, we found at most only a modest decline in the estimated heritability of GAD.

The Minimum Duration of GAD

Uncertainty remains about the optimal minimum duration for GAD. The 1-month minimum proposed in DSM-III was abandoned in DSM-III-R in part to better discriminate GAD from "transient stress reactions." The logic of this change, which implies that short episodes of GAD are entirely environmental in origin, is not supported by our findings, which suggest that genetic factors are at least as important in brief as in more prolonged episodes of GAD.

Common Environment and GAD

When 6-month GAD was diagnosed without hierarchy or with depression above GAD in the hierarchy, twin modeling suggested that twin resemblance resulted solely from familial environmental factors. How should this result, which is at odds with the findings for the remaining seven definitions of GAD, be interpreted? It may be a real finding, which suggests, counterintuitively, that genetic factors are important in brief episodes of GAD, and familial-environmental factors are important in more prolonged episodes of GAD. However, several points argue that this finding may be more plausibly due to stochastic fluctuation in small sample sizes. Far less confidence can be placed in the results with 6-month vs 1-month GAD because of the much smaller number of cases with the former than with the latter definition. A multiple threshold model, which formally posits that 6-month GAD belongs on the same liability dimension as shorter episodes of GAD, fits the data well. Finally, when panic is placed above 6-month GAD in a diagnostic hierarchy, the model fitting is again consistent with other findings in suggesting that twin resemblance for GAD is due to genetic and not familial-environmental factors.

GAD in MZ vs DZ Twins

Unexpectedly, when 1-month GAD was diagnosed without hierarchy, the risk for GAD was significantly greater in DZ than in MZ twins. Three hypotheses could explain this finding. First, GAD may have been associated with poor cooperation at the early stages of our survey, which, it can be shown, would produce lower rates of GAD in MZ vs DZ twins. Second, the close emotional bond between MZ twins may be a protective factor for GAD. Third, the finding may be due to chance. The plausibility of the first hypothesis is undermined by the finding of no consistent significant differences in rates of other psychiatric disorders in MZ vs DZ twins in our sample such as depression or alcohol dependence, which might also influence cooperation. We tested the second hypothesis by seeing if we could eliminate the difference in rates of GAD in MZ vs DZ twins by controlling for the closeness of the twin relationship as indexed by frequency of contact and strength of social support from the twin. While frequency of contact had no effect, the quality of social support from the twin reduced, but did not eliminate, the difference in rates of GAD in MZ and DZ twins. The lower risk for GAD in MZ vs DZ twins may result, in part, from the protective effect of the strong emotional bonding often seen in MZ twins. Other explanations, including stochastic variation, cannot, however, be ruled out, as zygosity effects were not consistently observed for other disorders, in particular major depression, where social support is also thought to be protective. Although we have not attempted to account for subtle effects of differing ascertainment rates for GAD in MZ and DZ twins, differences in base rates in the two zygosity groups have been incorporated into the analysis, as the tetrachoric correlations calculated separately in each group allow for different thresholds.

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Prevalence of GAD

As previously found by Breslau and Davis, the lifetime prevalence of GAD varied markedly as a function of the minimum required duration of illness. Increasing this duration from 1 to 6 months reduced lifetime prevalence in our sample by a factor of 4, similar to the fivefold reduction found by Breslau and Davis in an epidemiologic sample of female subjects. These results are in marked contrast to the findings from a clinical sample where most patients presenting with a GAD syndrome had symptoms for a large part of their lives. Epidemiologic and clinical samples of patients with GAD probably differ because individuals with short-duration GAD often do not seek professional help.

We are unaware of published lifetime prevalence rates for the DSM-III-R 6-month definition of GAD. Our lifetime prevalence rates for the 1-month GAD definition, which is close to the DSM-III criteria, are in the range previously found by others in female populations. Our rates (15% to 23%, depending on the hierarchy rules applied) are lower than the 45% reported by Breslau and Davis in mothers from Cleveland, Ohio, and the 35.1% reported by Wells et al. in a general population sample of female subjects from New Zealand, but higher than the rates of 5% to 12.4% found by Hwu et al. in female subjects from three different epidemiologic samples in Taiwan and the rates of 5.5% to 7.8% reported in female subjects from the various sites of the Epidemiologic Catchment Area study. In addition, our rates are similar to that of 18.8% found in a volunteer sample of men and women from the Australian National Health and Medical Research Council Twin Registry.

Limitations

These results should be interpreted in the context of four potentially significant limitations. First, these results apply only to female subjects. We do not know whether sex-specific transmission exists for GAD. However, preliminary evidence for a substantial difference in prevalence across sexes raises the possibility that genetic and environmental risk factors may differ in their impact on depression in male and female subjects.

Second, while based on a complete search of birth certificates, our final study sample is unlikely to be perfectly representative of the entire twin population. Twins who moved out of state or did not return earlier questionnaires were likely to be included in our sample. However, at least at the stage of personal interview, no relationship could be found between rate of GAD and cooperation of the cotwin.

Third, our results are, perforce, limited to twins. Could twins be atypical of the singleton population with respect to GAD? Previous studies have not found different rates of psychiatric disorder in twins vs singletons. Aside from the sequelae of their higher rate of obstetrical and perinatal complications, twins have been found consistently to be typical of the general population with respect to most traits, including levels of anxiety and depression. It cannot, however, be ruled out that our results are not generalizable to the nontwin population.

Fourth, a lifetime history of GAD was assessed in this study at a single point in time. The long-term test-retest reliability of such an assessment is unknown, but the experience with major depression suggests that it is far from perfect. Such unreliability of measurement, if uncorrelated in twin pairs, is, in our twin models, indistinguishable from the effects of individual specific environment. If longitudinal data were available in our twin sample, or we could “correct” for the effect of unreliability of measurement, the estimate of the heritability of GAD so obtained might be significantly higher than the one reported herein.

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References


