Brief Report

Association of Rapid Mood Switching With Panic Disorder and Familial Panic Risk in Familial Bipolar Disorder

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Objective: Comorbid bipolar and panic disorders aggregate in families. A phenotypic trait shared by both disorders is the sudden shift in affect observed in panic attacks and some rapid cycling states. The authors investigated whether comorbidity of bipolar disorder and panic disorder is associated with rapid mood switching in families with a high rate of bipolar disorder.

Method: Six hundred six subjects with bipolar disorder from the NIMH Bipolar Disorder Genetics Initiative were included in the study. Logistic regression analysis was used to analyze rapid mood switching as a function of panic disorder diagnosis, sex, and familial risk for panic.

Results: Familial panic and the diagnosis of panic disorder in an individual subject increased the odds for rapid mood switching. The familial effect persisted when individuals with panic disorder were excluded from the analysis.

Conclusions: Panic and rapid mood switching occurring together in familial bipolar disorder may define a useful subphenotype for future studies.

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Two independent family studies have produced evidence that bipolar and panic disorders may share genetic mechanisms (1, 2). The salient phenotype may thus be a trait common to both disorders. Panic attacks and rapid cycling states with fast polarity shifts both involve abrupt fluctuations in affective state (when anxiety is counted as an affect). There is tentative evidence of an association of both with a gene involved in catecholamine metabolism (3, 4). If there were a genetic trait for rapid affective shifts, one would predict familial aggregation of panic and bipolar rapid switching. Our aim was to discover whether rapid switching is associated with the familial aggregation of panic in families with a high rate of bipolar disorder.

Method

Background and detailed methodology for the NIMH Genetics Initiative are described elsewhere (5). Minimal entry requirements for a family were a treated proband with mania and at least one other first-degree relative with bipolar disorder, both at least 18 years of age. After giving written informed consent, all subjects included in this analysis were given the Diagnostic Interview for Genetic Studies (version 2.0) (6) by trained interviewers. Best-estimate diagnoses were made by two noninterviewing psychiatrists on the basis of the interview, available medical records, and family history data. For this analysis, we used Research Diagnostic Criteria (7) for major affective disorder diagnoses and DSM-III-R criteria for panic disorder.

In the course of the Diagnostic Interview for Genetic Studies, subjects completing the section on mania were asked whether they had "switched back and forth quickly between feeling high to feeling normal or depressed." Subjects' responses to this question became our dependent variable. Of the 718 individuals with bipolar disorder, 112 did not provide information about rapid mood switching and were excluded from the analysis. Of the 112 subjects who did not provide information on switching, 66 (59%) were never asked about rapid switching because the subject denied manic symptoms and, hence, interviewers bypassed that section. The remaining subjects completed the section but were unable to provide clear information about rapid mood switching.

TABLE 1. Selected Demographic Characteristics, Bipolar I Diagnosis, Panic Comorbidity, and Rapid Mood Switching in Subjects From Families With High Rates of Bipolar Disorder, Stratified by Familial Panic Comorbidity (N=606)

Variable	Low Panic[a]		Indeterminate Panic[b]		High Panic[c]		Total	
Number of families	56		76		76		208	
Number of subjects with bipolar disorder	133		215		258		606	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Characteristics of subjects with bipolar disorder								
Age at interview (years)	40.6	15.4	41.2	13.6	40.7	13.3	40.9	13.9
Age at onset of bipolar disorder (years)	20.1	8.7	20.5	9.2	19.6	9.1	20.0	9.1
	N	%	N	%	N	%	N	%
Female sex	71	53.4	130	60.5	163	63.2	364	60.1
Bipolar I diagnosis	105	78.9	159	74.0	194	75.2	458	75.6
Panic attack	0	0.0	83	38.6	146	56.6	229	37.8
Panic disorder	0	0.0	18	8.4	89	34.5	107	17.7
Rapid mood switching	41	30.8	90	41.9	137	53.1	268	44.2
Rapid cycling (four episodes in a year)[d]	45	34.4	92	43.2	127	50.6	264	44.4

[a] No family member with a bipolar disorder or recurrent major depression had panic attacks.
[b] Among family members with bipolar disorder or recurrent major depression, either only one relative had a panic attack or panic disorder or more than one had panic attacks but no one had panic disorder.
[c] Among family members with bipolar disorder or recurrent major depression, at least one had panic disorder and at least one other had panic attacks or panic disorder.
[d] As determined by an interview question answered by a total of 595 subjects with bipolar disorder; data on episode duration or remissions are not available.

Analysis

Logistic regression analyses were performed with generalized estimating equations (8), which appropriately account for potential correlations in the residual variation in the outcome (i.e., variation not explained by the model) among individuals from the same family. Thus, generalized estimating equations allow us to draw valid inferences from the data about the greater risk of rapid cycling in a family with panic. Statistical significance was defined as $p<0.05$ (two-tailed).

We characterized each family as having high, indeterminate, or low risk for familial panic on the basis of the number of family members with bipolar disorder (i.e., bipolar I, bipolar II with recurrent major depression, or schizoaffective-manic) or recurrent unipolar depression who had experienced panic. In the families characterized as "low panic" (N=56), no family member had experienced panic attacks. In the families characterized as "high panic" (N=76), one family member had panic disorder and at least one other family member had panic attacks or panic disorder. In the families characterized as "indeterminate panic" (N=76), only one family member had experienced panic disorder and no one else had panic attacks, or one or multiple family members had panic attacks but no one had panic disorder. Although this scheme has the disadvantage of favoring larger families in the high-panic than in the low-panic category (3.4 versus 2.4 members per family, respectively), in our experience this is the least problematic way to define familial aggregation (2). We tested the association of familial panic with rapid mood switching and included as covariates panic disorder (which appeared on inspection to be associated with rapid switching) and sex (female sex has been associated with both panic disorder and with rapid cycling [2, 9]).

Results

High-panic families had the highest proportion of subjects with rapid switching, and low-panic families had the lowest (Table 1). The odds ratio determined by logistic regression for rapid switching (N=606) was twice as high among individuals from high-panic families as in those from low-panic families (odds ratio=2.02, 95% confidence interval [CI]=1.24–3.29, z=2.83, $p<0.005$). Individuals from indeterminate-panic families had marginally elevated odds for rapid switching (odds ratio=1.50, 95% CI=0.93–2.42, z=1.66, p=0.10). Comorbidity of panic disorder and bipolar disorder in this model also significantly raised the odds of having rapid switching (odds ratio=1.83, 95% CI=1.15–2.92, z=2.54, p=0.01), but sex had no effect (odds ratio=1.07, 95% CI=0.76–1.50, z=0.38, p=0.70).

We repeated this analysis excluding subjects with comorbid panic disorder to evaluate whether familial panic and rapid switching were associated independently of an individual's diagnoses of panic disorder and obtained similarly significant results. Family size and antidepressant use also were found to have no confounding effect on the main results.

Two-thirds of the subjects with rapid switching had rapid cycling (i.e., four episodes in a year). When the analyses were rerun with rapid cycling as the outcome, the trends were similar but not statistically significant.

Discussion

High risk of panic in families with bipolar disorder was associated with rapid switching in family members who had bipolar disorder with or without comorbid panic disorder. Thus, panic in the context of familial bipolar disorder may derive from a familial trait, possibly genetic, that also contributes to rapid switching. To our knowledge, an association of panic disorder and rapid mood switching has not been reported in other data sets.

These results should be interpreted with caution because the interview question about rapid switching may have been interpreted inconsistently by subjects, although inconsistency was minimized because this question came

after thorough structured discussion about depressive and manic states. Uncertain subjects were excluded from this analysis. The large proportion of subjects missing data on rapid switching is another reason for interpretive caution.

Rapid switching may be equivalent to "ultradian" or "ultra-rapid cycling"; we lack the data to be able to apply these terms. We were unable to include in the analysis individuals with major depression, who might show an association of panic with rapid illness onset.

High acuity of symptom onset, as seen in both panic attacks and rapid polarity shifts, may be a phenotypic feature worthy of study by itself (10). This preliminary finding supports the prospect that biologically meaningful subtypes of bipolar disorder may in time become the standard for clinical diagnosis and treatment and for the identification of homogeneous phenotypes for research.

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