Anticipation of Age at Onset in Panic Disorder

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Objective: *Anticipation (i.e., the decrease in age at onset or the increase in severity of a disorder in successive generations) has recently been reappraised as a key to understanding the genetics of some familial illnesses. The purpose of this study was to search for possible anticipation in panic disorder.* *Method:* *Thirty-eight unilineal, multigenerational families with multiple directly interviewed members who had panic disorder were compared across two successive generations for 1) age at the first panic attack, 2) age at the onset of panic disorder, and 3) the highest degree of agoraphobia ever experienced, as a tentative index of severity of illness. Intergenerational pairwise comparisons were implemented according to four different sampling schemes: random pairs, random transmitting pairs, all possible pairs, and all possible transmitting pairs.* *Results:* *Life table analyses showed a significant decrease in the time before the first episode of panic and onset of panic disorder from the older to the younger generation. Evidence for anticipation was found for both indexes of onset in all four sampling schemes. No evidence of a generational effect on the index of severity of agoraphobia was found. Corrections for possible biases suggested that these results are not likely to be simple artifacts.* *Conclusions:* *Anticipation is supported in this specific set of families and, if it is confirmed by other studies, a role for trinucleotide repeat sequences may be considered to account for the familial aggregation of panic disorder.*

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Anticipation (i.e., the observed decrease in age at onset or increase in clinical severity in successive generations affected with the same illness) was initially described for neurological disorders such as myotonic dystrophy (1). Later investigation (2) showed that different sources of error may artifactually produce this effect, and anticipation was rejected as being a result of biased ascertainment of affected subjects. The recent finding that mutations of trinucleotide repeats are associated with anticipation, which is common to several disorders such as Huntington's chorea (3), has rehabilitated anticipation as a possible key to understanding the genetics of some illnesses, including the mental disorders (4).

Family studies (reviewed by Crowe [5]) show a strong tendency toward familial aggregation for panic disorder with agoraphobia, and data on twins (6, 7) confirm to different extents the importance of genetic factors in panic disorder. The mode of transmission is still unknown, and several candidate genes have been excluded by candidate gene probe and linkage studies (8); however, findings of transmission model studies based on ancestral pairs (9), segregation analysis (10), and sex-threshold analysis (11) were all compatible with a single-locus hypothesis. This background makes the search for possible anticipation in panic disorder worthwhile.

METHOD

This study was based on a group of 551 consecutive outpatients with panic disorder or panic disorder with agoraphobia who were

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seen over a period of 35 months at an anxiety treatment facility at San Raffaele Hospital, Milan. The group had a mean age at onset of panic disorder of 29.4 years (SD=9.7) and was an extension of a previous group of 231 patients, with the original recruitment and diagnostic methods (12) unchanged.

Briefly, initial family histories were obtained from the proband and one first-degree relative (in 78% of cases) by two psychiatrists (M.B. and Si.B.) using the Family History Research Diagnostic Criteria (FH-RDC) interview (13), adapted to generate DSM-III-R diagnoses by adding, as appropriate, the criteria from the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (14) used in the direct interview of the probands (12, 15).

Following the method of an earlier study of anticipation (16), we screened families for two or more siblings or one sibling and one parent of the index proband who had panic disorder or panic disorder with agoraphobia. The ascertained affected phenotypes included panic disorder, panic disorder with agoraphobia, and sporadic panic attacks.

After the exclusion of bilineally affected families through the family history interview and families in which key relatives were unavailable, there remained 82 families who were candidates for personal, blind interviews of first- and second-degree relatives with the appropriate section of the DIS. After complete description of the study to the subjects, written informed consent was obtained.

Family Study

In these 82 families, of the living first- and second-degree relatives of the index probands, 14% refused to be interviewed, 9% could not be located, and another 8% could not be interviewed for various reasons, including major physical illnesses or prolonged absence from their abode. As a consequence, only 75% of the living first-degree relatives could be interviewed at this phase of the study, and to gather information on unavailable relatives we used the FH-RDC interview with family informants.

The age at onset of panic disorder was defined as the age at which a proband first fully met the DSM-III-R criteria for panic disorder, and the age at the first attack was defined as the age at which a proband had first experienced an episode that met the DSM-III-R criteria for a panic attack. To rate the highest degree of severity of phobic avoidance ever experienced by the subject, as a tentative index of severity of illness, we used a questionnaire (17) with a semiquantitative rating scale ranging from 0 (absent) to 4 (severe).

The direct interviews with family members were made blind to the index proband's status and to information about the rest of the family. After the exclusion of families who showed evidence of bilineality at direct interview or who were without at least one personally interviewed affected person in each of two successive generations, there remained 38 families (81.6%, N=31, with multiple affected members) who met the minimal requirements for entering the study. In the 38 families, there was a total of 497 relatives. The mean number of first-degree relatives of the index probands was 5.7, and the mean number of second-degree relatives was 7.6. Affected subjects in the younger generation were sons, daughters, nephews, and nieces of affected subjects in the older generation.

There were 52 affected subjects (80% with panic disorder with agoraphobia and 20% with panic disorder) and 79 unaffected subjects in the older generation of relatives; 61.5% of the affected subjects in this generation were first-degree relatives of an index proband. The younger generation included 62 affected subjects (74% with panic disorder with agoraphobia, 13% with panic disorder, and 13% with sporadic panic attacks) and 76 unaffected subjects; 74.2% of the affected subjects in this generation were first-degree relatives of an index proband. For these 38 final families, direct interviews with 65% of all living first- and second-degree relatives (N=323) were obtained, while family histories from multiple informants were gathered for the remaining subjects (N=174).

Measures of Anticipation

The measures of anticipation were 1) age at the first panic attack, 2) age at onset of panic disorder, and 3) the highest degree of severity of agoraphobia ever experienced by the person interviewed. Analyses of age at the first panic attack and age at onset of panic disorder were made separately, because latencies of variable duration can occur between the first attack and the onset of the full-blown panic disorder. Most neuropsychiatric disorders have an insidious onset, but a panic attack (and the first attack especially) is sudden and unexpected. People can precisely date an attack, and interviewers show satisfactory agreement when rating the age at the first panic attack with the DIS (18).

The choice of an index of severity is less straightforward for panic disorder. We chose the highest severity of avoidance ever experienced, as it is an index of both social-interpersonal dysfunction (19) and severity of genetic liability (7, 11, 19), although it is subject to estimation biases linked to memory and recollection (18).

Sampling Schemes

Relatives in the same family do not constitute independent points of observation; this makes the choice of sampling schemes a complex task that is subject to several sources of bias. We chose the strategy of applying four different sampling schemes that generate different types of pairs of relatives (16), which has become widely used in studies of anticipation (16, 20, 21). In all four sampling schemes, probands who belonged to the younger generation were excluded from the analyses to avoid biases due to severity of illness as a primary cause for ascertainment, and only directly interviewed subjects were included in the analyses.

Each scheme has unique strengths and limitations (16), which we discuss briefly below.

1. Random pairs. In each family, one randomly chosen affected relative is selected from each generation to form a random pair (therefore, N=38 pairs in this study). This scheme is statistically conservative, and by allowing for the inclusion of childless members of the older generation in the pairs, it addresses the bias of a possible negative impact of early onset and higher severity of illness on fertility. However, only a proportion of the affected relatives are used in this scheme.

2. Random transmitting pairs. Only one randomly chosen affected parent is paired to one randomly chosen affected child in each family (again, N=38 pairs). This scheme most directly tests the hypothesis of anticipation of illness from the preceding generation to the following one, but childless members of the older generation are excluded. We had six families with neither parent affected. Like McInnis et al. (16), we arbitrarily assigned to these parents an age at the first panic attack and an age at onset of panic disorder equal to their age at interview and gave them a rating of 0 for severity of phobic avoidance.

3. All possible pairs. For each family, every affected member of the older generation is paired with every affected member of the younger generation to generate several possible pairs per family (in this case, a total of 55 pairs). Also, this sampling strategy includes childless affected members of the older generation in the analysis. It tests the robustness of the findings obtained by random pairs, but it has the limitation of multiple use of the same data points.

4. All possible transmitting pairs. Every affected parent in the older generation is matched with each of his or her affected children, which generated 39 pairs in our study. This scheme is again based on random pairs, but it is limited to actually transmitting pairs and tests the robustness of findings based on the random transmitting pairs.

In the pairwise comparisons for onset of the first panic attack, the number of all possible pairs was 54, and the number of all possible transmitting pairs was 41, as a consequence of the inclusion of subjects who had sporadic panic attacks at a frequency insufficient to meet the requirement for a DSM-III-R diagnosis of panic disorder.

Statistics

Age at onset in both the older and younger generations was normally distributed, while the severity of agoraphobia had a non-Gaussian distribution (as tested by Shapiro Wilks's W test). The mean current age of members of the older generation was 57.1 years (SD=9.9) and of the younger generation, 31.9 years (SD=8.1). The mean age at onset in the older generation was 36.3 years (SD=10.7) for panic dis-

FIGURE 1. Cumulative Percentage of Time Before Onset of Panic Disorder in Two Successive Generations of 38 Families

order and 35.8 years (SD=10.5) for the first panic attack. The mean age at onset in the younger generation was 22.7 years (SD=6.8) for panic disorder and 22.1 years (SD=7.1) for the first panic attack. Age at onset was compared between all members of the older generation and the younger generation by life table analysis and Gehan's generalized Wilcoxon test. Comparisons of age at onset and severity of agoraphobia in the pairs were made by nonparametric Wilcoxon matched-pairs statistics. All analyses were performed with the Statistica package (22).

RESULTS

Age at Onset Through Life Table Analysis and Duration of Illness

There was a marked difference in age at onset of panic disorder between members of the older and younger generations. The survival analysis showed a significantly earlier onset of panic disorder for members of the younger generation (Gehan-Wilcoxon test value= 3.5, p=0.0002) (figure 1).

The median duration of illness was 17 years for the subjects in the older generation and 5 years for the subjects in the younger generation, a significant difference (Kruskal-Wallis H=27.5, df=1, p<0.0001). In the older generation, 53.8% of the 52 affected subjects had received at least one medical treatment for panic disorder, and in the younger generation, 56.4% of the 62 affected subjects (χ^2=0.08, df=1, n.s.).

Pairwise Comparisons

In all pairwise comparisons, significantly earlier age at onset for members of the younger generation was consistently found (table 1). Anticipation of age at onset of panic disorder and of age at first panic attack, respectively, were observed in 88.2% and 90.7% of all possible pairs, 86.1% and 86.8% of random pairs, 94.9% and 95.1% of all possible transmitting pairs, and 94.4% and 92.1% of random transmitting pairs. When analyses were repeated after the exclusion of subjects with sporadic panic attacks, all differences remained significant. On the contrary, we found no significantly different severity of agoraphobia between the older generation and the younger generation (table 1).

We also looked for hints of imprinting (parental-origin influence on differential expression of genetic material). When offspring in all of the transmitting pairs were divided into two subgroups, one with affected fathers (N= 12) and the other with affected mothers (N= 27), no significant difference in the anticipation effect was found (Mann-Whitney U=140.5, p=0.50).

Corrections for Possible Biases

Indications of how one can appropriately address possible identified sources of bias have recently become available (16, 20, 23–30). A bias might derive from the diminished life expectancy of severely affected individuals in the older generation, who would be more likely to die young and less likely to be interviewed. On the basis of family histories from multiple informants, we found that four dead members of the older generation were likely to have had panic disorder. They were assigned an onset age of 23 years, corresponding to the mean age at onset for members of the younger generation. All differences in anticipation of age at onset remained significant (p=0.00002).

Members of the younger generation may have an apparent paucity of late-onset cases because they are younger at the time of observation; this would exclude a proband's siblings who may become ill at a later stage. To address this issue (16), unaffected members of the younger generation were assigned an onset age of 57 years, i.e., the mean current age of the members of the older generation. Even after this very conservative correction, age at onset remained significantly earlier in the younger generation than in the older generation (p=0.0007).

A recently recognized source of bias in anticipation studies is the differential age at interview of parent and child (29); however, a new method to control for this has recently been found (30). Briefly, the younger-generation subject's expected age at interview is compared with the observed age at interview (as the average of all the ages at onset in the older generation that are below the subject's age at interview), and then a paired t test is used to find out whether the difference is significantly higher than 0. After the application of this correction, anticipation remained significant: the observed mean age at onset in the younger generation for all pairs of relatives was 22.5 years (SD=7.3), and the expected mean age at onset was 24.6 years (SD=4.2) (t=3.20, df=54, p<0.002).

As first suggested by Penrose (2), pairs consisting of a parent with early age at onset and a child with late age at onset would be unlikely to be ascertained because of the time span separating the two onset events (23). Early-onset parents (defined as those with an age at on-

set ≤27 years, i.e., who are at least 2 years younger than the mean age at onset in the group of 551 outpatients with panic disorder) were present in 18% of the families. Among their offspring, 57% were already affected with panic disorder at the time of the study, and 70% of these had an earlier onset than that of their affected parent, with anticipation ranging between 1 and 11 years. Therefore, this bias should not have exerted a strong effect on this specific study group, even though only a lifetime follow-up of the offspring can definitely rule out such a possibility.

Another possible source of bias is the age cohort effect, or the tendency for an illness to show progressively earlier age at onset in successive birth cohorts. This has consistently been described for mood disorders in persons born after 1945 (31, 32). A large U.S. community survey (32), however, showed impressive stability of age at onset for panic disorder across different cohorts, which would therefore suggest the absence of an age cohort effect for this illness. One way to estimate control for the presence of a cohort effect on the difference in age at onset within parent-offspring pairs is to calculate the correlation between the difference in birth years and the difference in ages at onset within transmitting pairs (20); we found this to be nonsignificant in all possible transmitting pairs (r=–0.14, N=39).

TABLE 1. Pairwise Comparisons of Age at First Panic Attack, Age at Onset of Panic Disorder, and Severity of Agoraphobia According to Four Different Sampling Schemes in Two Generations of 38 Families

Variable and Sampling Scheme	Older Generation Mean	Older Generation SD	Younger Generation Mean	Younger Generation SD	Difference Mean	Difference SD	Analysis: z
Age at first panic attack (years)							
Random pairs	36.4	11.3	22.7	7.2	13.9	12.3	4.6*
Random transmitting pairs	40.7	12.7	22.2	7.6	18.2	11.2	5.2**
All possible pairs	34.8	10.7	21.5	6.8	13.4	11.1	5.7**
All possible transmitting pairs	39.7	12.9	21.9	7.5	18.0	10.8	5.4**
Age at onset of panic disorder (years)							
Random pairs	37.4	11.9	23.3	7.9	13.8	12.5	4.6*
Random transmitting pairs	39.7	11.2	22.2	6.6	16.9	10.9	5.1**
All possible pairs	35.2	11.2	22.5	7.1	12.5	11.7	5.7**
All possible transmitting pairs	38.7	11.5	21.9	6.5	16.3	11.0	5.1**
Severity of agoraphobia index							
Random pairs	1.4	0.9	1.5	1.0	–0.40	1.1	0.26
Random transmitting pairs	1.2	0.9	1.4	1.1	–0.15	1.1	0.85
All possible pairs	1.5	0.9	1.5	0.9	–0.09	1.1	0.53
All possible transmitting pairs	1.3	0.9	1.5	0.9	–0.47	1.2	1.09

*p=0.000005. **p<0.000001.

In mental disorders there may be an effect on the onset of an illness of the experience of being reared by an affected parent. To control for this we computed how many subjects in the younger generation had had their onset of illness before that of the older-generation parent. This proportion accounted for 21% of all possible transmitting pairs, a relatively high percentage if one takes into account the natural tendency of panic disorder to have its onset early in life.

Finally, the question of the so-called regression to the mean—i.e., the presence of a simple linear dependence in which the degree of anticipation gradually abates with the decreasing parental age at onset—was addressed. One way to re-propose the issue of regression to the mean (33) as applied to anticipation is to plot the difference between age at onset for parents and offspring (x–y) against the age at onset for parents (x) and see how they are related. Some authors think that the presence of regression to the mean in the form of a linear relationship between anticipation and parental age at onset strongly argues against a real phenomenon of anticipation; in one study (34) the hypothesis of "true" anticipation in schizophrenia was rejected because the authors observed a simple linear relationship between anticipation and age at onset in the parents, with a line of best fit very close to the one expected under the assumption that age at onset in offspring was normally distributed around the mean. Hodge and Wickramaratne (28) have shown that anticipation and correlation of ages at onset between parents and offspring are two independent phenomena, and that regression analysis does not contribute to discriminating "true" anticipation from an effect due to ascertainment bias. It has also been argued by other authors (4, 25) that regression to the mean does not exclude "true" anticipation, and McInnis et al. (24) showed how for a set of randomly generated values of x and y, the correlation between x and x–y is significantly high, and the x intercept where x–y=0 coincides with the mean for the values of x. In our study group the regression coefficient of anticipation correlation between x and x–y is as high as 0.69 (F=34.07, df=1, 37, p=0.000001), but the x intercept is at 26.2, well below the mean of parental age at onset (36.3 years) and thus in contradiction with the expectancy of Galtonian regression to the mean (33).

The study was designed to minimize possible biases related to clinical severity as a primary cause for ascertainment (subjects with associated features of alcohol/substance abuse, which perhaps indicates greater severity and earlier onset, were excluded from the study, and index probands in the younger generation were excluded from analyses), possible biases related to additive genetic effects from both parental lines on the younger generation (all families with evidence of bilineality were excluded from the study), and possible biases related to preferential ascertainment of late-onset parents due to possible diminished fertility of early-onset patients (childless members of the older generation were included in the sampling schemes).

DISCUSSION

Anticipation of age at first panic attack and age at onset of panic disorder is suggested in these 38 unilineally affected pedigrees examined with different sampling schemes. Given the results of the corrections for possible biases, this finding may not be simply an artifact. Moreover, it is in harmony with a previous report (12) that age at onset is significantly affected by a family history of panic disorder with agoraphobia. The mean ages at onset of panic disorder for subjects in the younger generation (23 years) and the older generation (36 years) diverge almost symmetrically (6 years and 7 years) from the mean age at onset in the group of consecutive outpatients from which the index probands were drawn (29 years).

Neither a significant generational effect on the degree of severity of agoraphobia nor evidence for imprinting was found. However, the same has been reported for several neuropsychiatric disorders (4) and some unstable trinucleotide diseases (4) in which anticipation has been demonstrated. Although these inconsistencies are somewhat confounding (evidence of imprinting and increase in severity may corroborate a finding of anticipation), several authors accept that anticipation can still be true in such cases (4, 30). For instance, of two recent studies of anticipation in schizophrenia, one (21) found no intergenerational effect on clinical severity, and the other (30) neither found evidence for imprinting nor assessed possible increase of clinical severity between generations, but the authors concluded that anticipation was demonstrated in the families. While there is convincing evidence that panic disorder with agoraphobia is a more severe variant of panic disorder (19) that tends to segregate within families of probands who have homotypic disorders (7, 12), the index of clinical severity selected for this study may have been unsatisfactory for several different reasons. Possible explanations include biases in memory and recollection of symptoms of avoidance, given the natural tendency of the disorder to show periods of remission and/or given the methodologic difficulties of defining the degree of avoidance (a relative insensitivity of the measure). Alternatively, it may be that agoraphobia as a category (i.e., present or absent) identifies a more severe expression of the illness (7) without enough additional variance to further characterize the level of severity. However, if agoraphobia in panic disorder increases as a function of the duration of illness and repeated occurrence of panic attacks, and it is ameliorated by treatment (35), one might expect that in a cross-sectional study group with the same frequency of treated subjects in the two generations, the younger generation would show a milder degree of agoraphobia because of their shorter history of illness. Our negative result for the severity of agoraphobia is at variance with this expectation, and this might reflect a simple effect of time on the severity of avoidance.

A possible recall bias for age at onset also should be considered, since the estimation is obtained through patients' reports at interview, and some data suggest that older respondents may report only recent symptoms, thus yielding falsely high age at onset (36). Analyses of the Epidemiologic Catchment Area data, however, show no such tendency for older respondents with panic disorder (32). Another study, which accurately considered the interval between current age and age at onset of depression (37), showed good reliability of reported age at onset and found that older respondents tended in fact to systematically decrease, and not increase, reported age at onset across two observation times.

Other possible limitations should be borne in mind. This study group was far from a community sample. Index probands were drawn from an anxiety treatment facility, and families were selected for the uncommon features of being unilineally and multiply affected in two generations. Such families may be relatively rare in the population or in clinical practice. On the other hand, the numbers of pairs generated by the all possible pairs scheme and the all possible transmitting pairs scheme are relatively small compared with those in other studies of anticipation (16), but it should be remembered that we used a quite restricted definition of spectrum of liability to panic disorder, an illness per se that is relatively uncommon in the population.

Only a limited proportion of subjects in the younger generation had had their onset before that of the older-generation parent, which leaves some possible role for nongenetic factors to partially account for the observed anticipation. Unfortunately, no adoption study of panic disorder that would appropriately address this question has so far been published.

Although the sampling schemes adopted here have been used previously to clarify the possible presence of anticipation in bipolar illness and schizophrenia (16, 21), they may not be considered optimal by other researchers in the field.

Despite the popularity of the trinucleotide repeats model in explaining the transmission of several illnesses, it should be remembered that the genetic-epidemiologic phenomenon of anticipation needs be distinguished from the molecular mechanism (38), and that evidence for anticipation can best be demonstrated after the genes have been found (29).

All of these aspects, in addition to the fact that reporting of anticipation in panic disorder is unprecedented, suggest that larger samples and replication studies are needed. If confirmed, these results indicate that genes embodying trinucleotide repeats may be involved in the familial transmission of panic disorder.

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