

Age at Onset of Panic Disorder: Influence of Familial Liability to the Disease and of Childhood Separation Anxiety Disorder

Marco Battaglia, M.D., Silvana Bertella, M.D., Ernestina Politi, M.D.,
Luana Bernardeschi, M.D., Giampaolo Perna, M.D.,
Angela Gabriele, M.D., and Laura Bellodi, M.D.

***Objective:** The authors investigated the relation of age at onset of panic disorder to liability to panic disorder and agoraphobia. **Method:** Two hundred thirty-one outpatients with panic disorder were compared with 131 surgical outpatients on demographic variables and familial risk of psychiatric disorders. The distribution of patients' ages at onset of panic disorder and several covariates were entered in a stepwise survival analysis. **Results:** The patients with panic disorder had a significantly higher rate of childhood separation anxiety disorder and higher familial risks of panic disorder/panic disorder with agoraphobia and alcoholism. A family history of panic disorder with agoraphobia and the presence of childhood separation anxiety disorder influenced age at onset of panic disorder. **Conclusions:** Age at onset of panic disorder may reflect genetic penetrance, and separation anxiety disorder may be an individual predictor of earlier onset of panic disorder.*

(Am J Psychiatry 1995; 152:1362-1364)

In illnesses of multifactorial origin, patients with early onset often have the more severe expressions of the diseases, and their relatives are more likely to have the same disorders than the relatives of patients with late onset, perhaps reflecting augmented penetrance, etiological heterogeneity, or both (1). We investigated the relation of age at onset to familial liability to panic disorder with agoraphobia and to other familial, clinical, developmental, and demographic variables, assuming that if a significant effect of family history could be found, then age at onset could be used for a better understanding of the genetics of panic disorder.

METHOD

The subjects were 231 consecutive outpatients with panic disorder or panic disorder with agoraphobia who were seen over a period of 15 months at an anxiety treatment facility at San Raffaele Hospital, Milan, all of whom gave informed consent. Previous clinical di-

agnoses of panic disorder were independently confirmed (97% concordance) by residents in psychiatry who administered the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (2) (for panic disorder with agoraphobia, mean kappa=0.88). A history of drug abuse/dependence or alcoholism (rate=14%) was an exclusion criterion. Separation anxiety disorder was retrospectively and independently diagnosed by means of a DSM-III-R symptom checklist (3). The DIS and the checklist for separation anxiety disorder were also used to interview a comparison group of 131 surgical outpatients.

Family histories were obtained from the proband and one first-degree relative (73% of cases) for 1,086 first-degree relatives of the patients with panic disorder and 660 relatives of the surgical patients by two psychiatrists (for panic disorder/panic disorder with agoraphobia in 55 independently ascertained pedigrees, kappa=0.70). The psychiatrists used the Family History Research Diagnostic Criteria interview (4), adapted to generate DSM-III-R diagnoses by adding, as appropriate, the DIS criteria used in the direct interviews of the probands. Only cases rated as definite were considered. Morbidity risk rates for panic disorder and major depression were age-corrected (5) with a suitable computer program based on Cox's model (6), as was done in previous studies (1, 7), while risk rates for antisocial personality (ages at risk=10-18 years), alcoholism, and drug abuse (ages at risk=15-39 years) were computed by Weinberg's abridged method (8).

The distribution of ages at onset among the patients with panic disorder was analyzed by the stepwise method of survival analysis with the BMDP statistical package 2L procedure (9). Age at onset was the dependent variable; independent covariates were 1) sex, 2) presence or absence of agoraphobia, comorbid major depression (lifetime), and history of childhood separation anxiety disorder, and 3) presence or absence of a family history of panic disorder without agoraphobia, panic disorder with agoraphobia, major depression, alcoholism, and antisocial personality disorder.

Received Oct. 17, 1994; revision received Feb. 16, 1995; accepted April 6, 1995. From the Istituto Scientifico H. San Raffaele. Address reprint requests to Dr. Battaglia, Istituto Scientifico H. San Raffaele, Department of Neuropsychiatric Sciences, University of Milan School of Medicine, 29 via Prinetti, 20127 Milan, Italy.

The authors thank Drs. Angelo Bertani, Cinzia Arancio, Valerio Sansone, and Giorgio Guazzoni for collaboration in data collection.

TABLE 1. Demographic and Clinical Characteristics of Patients With Panic Disorder and a Comparison Group of Surgical Patients

Item	Panic Disorder Patients						Surgical Patients					
	Female (N=173)		Male (N=58)		Total (N=231)		Female (N=73)		Male (N=58)		Total (N=131)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	36.6	12	34.5	11	36.3	11	38.8	13	35.2	11	37.3	12
Age at onset of panic disorder (years)	29.4	10	28.2	10	29.1	10	14.0	—	34.0	—	24.0	14
	N	%	N	%	N	%	N	%	N	%	N	%
DSM-III-R diagnosis												
Panic disorder	173	100.0	58	100.0	231	100.0	1	1.4	1	1.7	2	1.5
Major depression	35	20.2	5	8.6	40	17.3	11	15.1	4	6.9	15	11.5
Social phobia	31	17.9	7	12.1	38	16.5	9	12.3	5	8.6	14	10.7
Simple phobia	24	13.9	8	13.8	32	13.9	9	12.3	5	8.6	14	10.7
Antisocial personality disorder	0	0.0	3	5.2	3	1.3	0	0.0	0	0.0	0	0.0
Childhood separation anxiety disorder ^a	65	37.6	21	36.2	86	37.2	12	16.4	5	8.6	17	13.0

^aSignificantly more common among patients with panic disorder than among surgical patients ($\chi^2=22.9$, $df=1$, $p<0.001$).

RESULTS

Table 1 shows demographic and clinical characteristics of the subjects. Childhood separation anxiety disorder was diagnosed significantly more frequently among the patients with panic disorder.

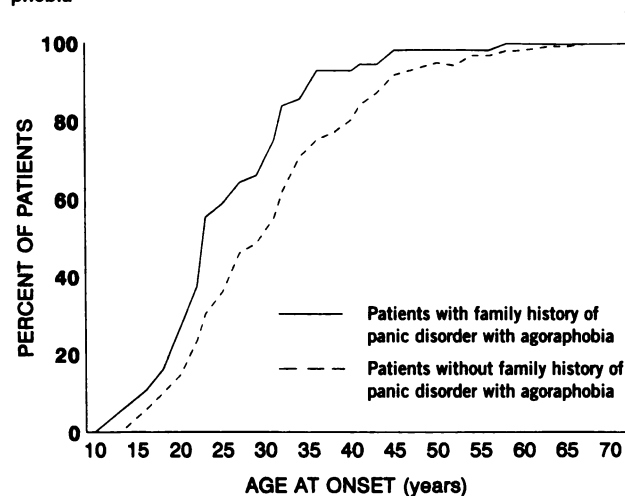
The patients with panic disorder had significantly higher familial risks of panic disorder/panic disorder with agoraphobia and alcoholism than the surgical patients who did not have panic disorder. The risk of panic disorder with agoraphobia was 7.6% (64/839.1) and 1.0% (5/476.2), respectively (test of the difference between two proportions: $Z=5.04$, $p<0.001$); the risk of alcoholism was 6.2% (39/626.5) and 1.7% (6/354.0), respectively ($Z=3.20$, $p=0.002$).

Fifty-six patients had family histories of panic disorder/panic disorder with agoraphobia; the mean age of their relatives (one relative per proband, randomly chosen) was slightly lower than that of the relatives of the 175 patients without such a family history: 45 years ($SD=16$) versus 48 years ($SD=14$) ($t=1.1$, $df=229$, *n.s.*). The mean number of individuals in the families of both groups of subjects was five ($SD=2.2$). The familial risk of panic disorder/panic disorder with agoraphobia was similar for the patients with panic disorder with a history of separation anxiety disorder and those without such a history: 8.9% (22/247.5) and 7.1% (42/591.6), respectively).

In the stepwise analysis applied to survival analysis with covariates, only two of the several independent variables significantly affected the age at onset of panic disorder in the regression procedures, namely, a family history of panic disorder with agoraphobia (log-likelihood=-739; improvement $\chi^2=8.8$, $df=1$, $p=0.003$; global $\chi^2=9.9$, $df=1$, $p=0.002$) and the presence of separation anxiety disorder in childhood (log-likelihood=-736; improvement $\chi^2=5.7$, $df=2$, $p=0.02$; global $\chi^2=15.8$, $df=2$, $p<0.001$).

Figure 1 shows the age at onset curves for the pa-

FIGURE 1. Distribution of Ages at Onset of Patients With Panic Disorder With or Without a Family History of Panic Disorder With Agoraphobia



tients, with family history of panic disorder with agoraphobia as the only independent variable.

DISCUSSION

The presence of familial panic disorder with agoraphobia—and no other familial-genetic variable—influenced age at onset of panic disorder. This finding suggests a specific relationship between age at onset and familial-genetic loading for panic disorder with agoraphobia as well as a possible penetrance effect, because panic disorder with agoraphobia segregates specifically among relatives of patients with panic disorder with agoraphobia (7), and it is a likely index of severity of genetic liability to panic disorder (7, 10). A methodologically different preliminary study (11) reported similar results.

Childhood separation anxiety disorder was also associated with earlier onset in our study. Although separation anxiety disorder is diagnostically distinct from panic disorder (12, 13), the two disorders may be linked to each other by common, underlying neurophysiological vulnerability (13), and some data suggest that separation anxiety disorder may also be an indicator of familial liability to panic disorder with agoraphobia (12, 14). Since we found that separation anxiety disorder was associated with earlier onset of panic disorder, our data suggest that separation anxiety disorder may be an individual risk factor, but they fail to provide evidence that it may also be a familial indicator of liability to the illness, since the familial risk of panic disorder with agoraphobia is similar for patients with panic disorder who have a history of separation anxiety disorder and those without such a history.

Our relying on patients' memories, including the retrospective diagnosis of separation anxiety disorder, is a possible limitation of this study. While the ages at onset of panic disorder were within the range of values usually reported, some patients' accounts may have been inaccurate. If such uncontrolled bias exists, however, the error should be random.

A second limitation is that the patients were drawn from an anxiety treatment facility, and some of the comorbidity figures may not be entirely applicable to subjects seen in other contexts. The family history method constitutes another limitation because of its insensitivity and bias toward within-family diagnostic homogeneity. However, the findings on familial risk are in keeping with those in studies of patients with panic disorder with low rates of comorbid depression and/or no comorbid alcoholism (7, 14).

We conclude from this study that age at onset can be an indicator of genetic penetrance of panic disorder, as

has been found for other disorders of possible multifactorial origin.

REFERENCES

1. Smeraldi E, Gasperini M, Macciardi F, Bussoleni C, Morabito AS: Factors affecting age at onset in patients with affective disorders. *J Psychiatr Res* 1983; 17:309-317
2. Robins LN, Helzer JE, Cottler L, Golding E: National Institute of Mental Health Diagnostic Interview Schedule, version III, revised. St Louis, Washington University, 1989
3. Van der Molen GM, Van Den Hout MA, Van Dieren AC, Griez E: Childhood separation anxiety and adult onset panic disorder. *J Anxiety Disorders* 1989; 3:97-106
4. Andreasen NC, Rice J, Endicott J, Reich T, Coryell W: The family history approach to diagnosis: how useful is it? *Arch Gen Psychiatry* 1986; 43:421-429
5. Heimbuch RC, Matthyse S, Kidd KK: Estimating age-of-onset distributions for disorders with variable onset. *Am J Hum Genet* 1980; 32:564-574
6. Cox DR: Regression models and life tables. *J R Stat Soc* 1981; 34:187-220
7. Gruppo Italiano Disturbi d'Ansia: Familial analysis of panic disorder and agoraphobia. *J Affect Disord* 1989; 17:1-8
8. Stenstedt A: A study in manic depressive psychosis. *Acta Psychiatr Neurol Scand* 1952; 79:1-111
9. Dixon WJ (ed): BMDP Statistical Software Manual to Accompany the 7.0 Software Release, vols 1-3. Berkeley, University of California Press, 1992
10. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ: Panic disorder in women: a population-based twin study. *Psychol Med* 1993; 23:397-406
11. Goldstein RB, Wickramaratne PJ, Horwath E, Weissman MM: Familial Aggregation of Early-Onset (Less Than 20 Years) Panic Disorder. *Neuropsychopharmacology Suppl* 1994; 28
12. Moreau D, Weissman MM: Panic disorder in children and adolescents: a review. *Am J Psychiatry* 1992; 149:1306-1314
13. Klein DF: False suffocation alarms, spontaneous panics, and related conditions: an integrative hypothesis. *Arch Gen Psychiatry* 1993; 50:306-317
14. Weissman MM: The epidemiology of anxiety disorders: rates, risks and familial patterns. *J Psychiatr Res* 1988; 22(suppl 1):99-114