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Research report

Differential clinical features of early-onset panic disorder

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Abstract

Background: Although panic disorder (PD) begins typically in adulthood, an earlier onset is not uncommon. Recent studies on early-onset PD indicate that this subgroup of patients may display distinct clinical characteristics. *Objective:* To compare a subgroup of early-onset PD patients with the rest of the sample. *Method:* A consecutive series of 442 patients with PD were included. Family histories were investigated, and clinical assessment employed the following instruments: Hamilton's scales, Global Functioning Scale, Marks-Mathews' Fears and Phobia Scale, and Panic-Associated Symptom Scale. The age threshold for 'early-onset' was considered at 18 years. *Results:* A total of 45 patients (10.2%) exhibited early-onset PD, with a mean age at onset of 14.6. They were younger and had a longer duration of illness than later-onset patients. No differences were found in severity of panic symptoms, anxiety or depressive symptoms, and social functioning. They had more comorbidity with simple phobia, social phobia, and substance dependence. Rates of PD among first-degree relatives were higher in the early-onset group. *Conclusion:* Early-onset PD patients displayed a greater familial loading, but clinical severity of their panic-agoraphobia symptoms was not higher. Comorbidity was greater with phobic and substance-related disorders.

Keywords: Panic disorder; Early-onset; Familial loading; Social phobia

1. Introduction

Panic disorder (PD) is a common psychiatric condition. Its lifetime prevalence rates which have been found to be similar throughout the world, are estimated to range from 1.4% to 3.8% of the general population (Regier et al., 1990; Katerndahl and Realini, 1993; Eaton et al., 1994; Weissman et al., 1997). It is 2–3 times more common in women than in men, and females are at greater risk of developing agoraphobia or major depression (Weissman et al., 1997). An epidemiological study conducted in Spain employing the SCID for DSM-III-R found a point prevalence of 4.1% (Gago, 1992).

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The disorder begins most typically in late adolescence or early adulthood (between 25 and 35 years of age). PD with an onset in childhood or adolescence has been the subject of fewer studies than adult-onset PD. Recent retrospective studies in adults suggest that panic attacks may begin in childhood (Sheehan et al., 1981; Breier et al., 1984). The first reports of PD in childhood and adolescence, which date back to 1987 (Casat et al., 1987; Vitiello et al., 1987; Biederman, 1987; Alessi et al., 1987; Ballenger et al., 1989; Moreau et al., 1989; Black and Robbins, 1990; Vitiello et al., 1990; Black et al., 1990), were flawed with several methodological problems: small inpatient samples, non-standardized assessment procedures, few sources of information, lack of assessment of panic severity, or lack of distinction between cued and uncued attacks (Klein et al., 1992; Kearney and Silverman, 1992). Further research has concluded that PD is rare in the prepubertal period (Ollendick et al., 1994; Kearney et al., 1997), that panic attacks are common in adolescence (11–13%) (Hayward et al., 1989; Macaulay and Kleinknecht, 1989; Telch et al., 1989), and that prevalence rates in adolescents are somewhat lower than in adults, ranging from 0.6% to 1% (Whitaker et al., 1990; Lewinsohn et al., 1993). These results suggest that panic attacks during adolescence might precede panic attacks in adulthood. Thus, Eaton et al. (1995), in their reanalysis of the ECA study, found that the prodromal period prior to the onset of PD lasted 10 years, with 20% of subjects reporting their first panic attack at about age 14 and 50% before age 20, although the mean age at onset was 24.87 years.

Clinical characteristics of PD at earlier ages appear to be similar to those found in adults (Moreau and Weissman, 1992). What remains to be determined is whether earlier-onset PD (onset before 20 or 25 years of age for some authors) is a specific PD subtype, since it has been found to have greater familial risk (Goldstein et al., 1997; Battaglia et al., 1995), distinct phenomenology (Wittchen and Perkonigg, 1993), different comorbidity (Goldstein et al., 1997; Wittchen and Perkonigg, 1993), more clinical severity (Goldstein et al., 1997), and higher suicide risk (Weissman et al., 1989).

In the present study, we sought to analyse the clinical characteristics of subjects with early-onset PD, and compare them to those of patients with later-onset PD.

2. Method

2.1. Study setting

The study was conducted at two mental health centres in Barcelona (northeastern Spain). The first setting is the psychiatric unit of the hospital of La Alianza, a 450-bed general hospital associated to Barcelona University, which belongs to a Health Maintenance Organization (HMO) serving a population of 210 000 (La Alianza also owning five hospitals in smaller towns in Calatunya). The other setting (PSINEP) is a neuropsychiatric clinic that provides standard outpatient psychiatric care. Both centres belong to the private health sector, and serve 24% of the area population. Nearly 10% of the patients attending at La Alianza were referred from the Social Security, as this hospital has a contract with the Public Health system. Care was provided by the same team of clinicians at both settings. Starting with the creation of both units, the study lasted 4 years (from March 1991 to February 1995). During this period, 3206 patients were seen at La Alianza, and 2095 patients at PSINEP.

2.2. Subjects

All patients diagnosed with PD were enrolled into the study. All of them were new patients, consecutively assessed starting with the creation of the two new psychiatric clinics. Subjects were excluded if PD was due to a general medical condition or associated with organic brain disorders, in accordance with DSM-III-R criteria. Thyroid tests were conducted on all patients, as well as an EKG, a chest X-ray and a neurological examination. The study was approved by the hospital's Ethics Committee, and participation consent was obtained from the patients. Of the 5301 patients examined at the two centres over the 4 years, 8.3% exhibited a diagnosis of PD. The rate was slightly higher at La Alianza (274 out of 3206; 8.5%) than at PSINEP (168 out of 2095; 8%). The study sample represented a series of 442 patients affected of PD, aged 16 years or older. The average age of the sample was 40.73 years (S.D. = 14.57 years), 76.4% were females, 65.61% were married, and the mean age at PD onset was 32.83 years (S.D. = 18.83 years).

2.3. Procedure

Clinical assessment was conducted by two experienced interviewers, a psychiatrist (J.S.) or a clinical psychologist (J.C.), following DSM-III-R criteria. The Structured Clinical Interview for DSM-III-R Upjohn Version Rev. (SCID-UP-R) was used for Axis I diagnoses (Spitzer and Williams, 1988). The presence of comorbid psychiatric disorders was also studied, following DSM-III-R criteria. Owing to the reduced number of patients within some diagnostic categories, diagnostic groupings were made for drug dependencies (which included alcoholism and other drug dependencies) and for eating disorders (which included anorexia and bulimia nervosa). For the same reason, diagnoses of schizophrenia (one case), bipolar disorder (four cases), and somatization disorder were also not included as comorbid disorders. Comorbid diagnostic reliability was checked by two independent evaluators in a group of 30 patients, obtaining a κ coefficient of 0.8 for Axis I diagnoses.

The Family History Research Diagnostic Criteria interview (Endicott et al., 1975) in its Spanish version (Humbert, 1989) was used to assess the patients' family history. Patients or their first-degree relatives were the source of information for assessing psychiatric family histories.

To assess clinical severity, evaluation at the first visit included the administration of the Hamilton's anxiety and depression scales (HDRS and HARS) (Hamilton, 1959, 1961), the Global Functioning Scale (GAF) (American Psychiatric Association, 1987), the Marks-Mathews' Fears and Phobia Scale (Marks and Mathews, 1979), and the Panic-Associated Symptom Scale (PASS) (Argyle et al., 1991).

In addition, we used a 14-item inventory of panic attack symptoms based on DSM-III-R symptoms. This self-administered inventory rates on a 4-point Likert scale to assess the severity of symptoms (0 = non-existent; 1 = mild; 2 = moderate; 3 = severe). Patients over 60 years, or whenever cognitive dysfunction was suspected, completed as well the Spanish version (Lobo et al., 1979) of the Mini-Mental Status Examination (Folstein et al., 1975).

A group of 162 patients completed the Symptom Checklist-90 (SCL-90) (Derogatis, 1977), the Eysenck Personality Questionnaire (Junior and Adult) (Eysenck and Eysenck, 1975) in its Spanish version (Escolar, 1981), and the Spanish version of the Susceptibility to Punishment Scale (Escala de Susceptibilidad al Castigo, Torrubia and Tobeña, 1984), which is a 30-item scale based on Gray's construct of 'susceptibility to punishment'.

2.4. Data analysis

Patients with PD were divided into two groups on the basis of age at PD onset: 'early-onset' was fixed at 18 years of age or under, and 'later-onset' over 18 years. The choice of age 18 as a cut-off point was arbitrary, suggested by the threshold age of pediatric care in our country.

The statistical tests used were Student's *t*-test for continuous variables, and χ-square test for categorical variables, applying Yates' correction or Fisher's test where necessary. The minimum level of significance was set at $p < 0.05$. The odds ratios (OR) were obtained by logistic regression, with a confidence interval of 95%. OR, which indicate the strength of association among comorbid psychiatric diagnoses in both groups, are statistically significant when the confidence intervals include 1.0. The data analyses were performed by using the SPSS software package (Norusis, 1990).

3. Results

Forty-five patients (10.2% of the sample) displayed early-onset PD. Their mean age at onset was 14.6 years (S.D. = 2.47), vs. 34.9 years (S.D. = 13.1) in the later-onset group ($p < 0.001$). Early-onset PD patients were younger ($p < 0.001$) and had a higher educational level ($p < 0.05$).

3.1. Psychiatric family history

The early-onset PD group had higher rates of PD among first-degree relatives ($p < 0.05$). No differences were found with respect to depression, schizophrenia and alcohol dependence (Table 1).

3.2. Clinical features

The clinical course was longer in early-onset PD patients. No differences were observed between both groups with respect to medical or psychiatric ser-

Table 1
Sociodemographic characteristics

	< 18 years ($n = 45$)	> 18 years ($n = 397$)	Significance
Female sex	36 (80.0%)	301 (75.8%)	n.s.
Current age (years)	29.2±11.43	41.98±14.3	$p < 0.001$
Educational level (years)	11.0±3.46	9.56±3.74	$p < 0.05$
	1 (2.2%)	23 (5.8%)	
Family history			
Alcoholism	8 (17.8%)	36 (9.1%)	n.s.
Panic disorder	16 (35.6%)	84 (21.2%)	$p < 0.05$
Schizophrenia	1 (2.2%)	5 (1.3%)	n.s.
Depression	16 (35.6%)	99 (24.9%)	n.s.

vices utilization (emergency room or scheduled visits, hospitalizations, medical care for suicide attempts). Also, we did not find differences in anxiety or depression scores (Hamilton's rating scales), social functioning (GAF), or severity of panic symptoms (PASS). With regard to panic attack symptoms, patients with early-onset PD were more likely to report depersonalization than later-onset PD patients (42.2% vs. 27.5%, $p < 0.05$), whereas similar rates were found for all other symptoms (Table 2).

We found early-onset PD to be more frequently associated with social phobia, simple phobia, and substance dependence than later-onset PD (Table 3). The greater comorbidity with phobic disorders accounts for the higher scores in the subscales of social phobia ($p < 0.05$) and blood phobia ($p < 0.05$) in the Marks-Mathews' Questionnaire.

Table 2
Clinical characteristics

	< 18 years ($n = 45$)	> 18 years ($n = 397$)	Significance
Age panic onset (years)	14.58±2.47	34.88±13.05	$p < 0.001$
Course (years)	14.64±11.86	7.10±9.70	$p < 0.001$
Number of attacks (last month)	10.93±15.93	11.94±14.5	n.s.
Medical visits	41 (9.1%)	360 (90.7%)	n.s.
Emergency room visits	17 (37.8%)	159 (40.1%)	n.s.
Psychiatric visits	17 (37.8%)	162 (40.8%)	n.s.
Prior admissions	4 (8.9%)	86 (6.5%)	n.s.
Prior suicide attempts	4 (8.9%)	18 (4.5%)	n.s.
HDRS	18.20±8.04	17.90±7.7	n.s.
HARS	24.70±7.00	23.50±6.6	n.s.
GAF	54.70±6.60	56.20±6.70	n.s.
Marks and Matthews fears and phobia scale			
Social	7.38±9.83	3.61±7.60	$p < 0.05$
Blood	12.20±9.70	9.11±8.25	n.s.
Agoraphobia	13.84±12.50	15.50±13.20	n.s.
PASS (total)	15.70±5.71	4.90±5.80	n.s.
Situational anxiety	2.87±1.83	2.67±1.86	n.s.
Spontaneous anxiety	4.18±1.15	4.18±1.24	n.s.
Limited anxiety	4.58±1.63	1.19±1.21	n.s.
Anticipatory anxiety	4.89±1.64	4.52±1.72	n.s.
Phobias	2.38±1.58	2.40±1.71	n.s.

Table 3
Panic disorder comorbidity

	< 18 years ($n = 45$)	> 18 years ($n = 397$)	OR[a]	CI[b]	Significance
Major depression	14 (31.1%)	145 (36.5%)	1.27	0.65–2.47	n.s.
Eating disorders	3 (6.7%)	11 (2.8%)	0.39	0.67–9.33	n.s.
Drug dependency	10 (22.2%)	36 (9.1%)	2.85	1.31–6.23	$p < 0.01$
Obs.-Comp. disorder	4 (8.9%)	27 (6.8%)	0.74	0.45–4.00	n.s.
Specific phobia	21 (46.7%)	111 (28.0%)	2.27	1.20–4.21	$p < 0.01$
Social phobia	13 (28.9%)	52 (13.1%)	2.70	1.33–5.45	$p < 0.01$
Agoraphobia	38 (84.4%)	313 (78.8%)	0.68	0.63–3.40	n.s.

[a] Odds Ratio.
[b] Confidence Interval.

Table 4
SCL-90, susceptibility to punishment and EPQ in 162 PD patients

	< 18 years ($n = 21$)	> 18 years ($n = 141$)	Significance
SCL-90-R			
Somatization	1.31±0.72	1.31±0.78	n.s.
Obs-Comp.	1.80±0.92	1.63±0.93	n.s.
Int. sensitivity	1.62±0.91	1.17±0.84	$p < 0.05$
Depression	1.72±1.06	1.53±0.96	n.s.
Anxiety	1.98±0.96	1.64±0.94	n.s.
Hostility	1.44±1.15	0.86±0.79	$p < 0.05$
Phobia	1.22±0.93	1.30±1.00	n.s.
Paranoia	1.44±0.94	1.09±0.93	n.s.
Psychoticism	1.10±0.76	0.74±0.73	$p < 0.05$
GSI	1.53±0.73	1.28±0.71	n.s.
Susceptibility to punishment	23.05±5.51	21.03±6.09	n.s.
EPQ			
Neuroticism	20.00±3.01	7.83±4.98	$p < 0.01$
Extraversion	8.82±4.87	9.60±4.40	n.s.
Psychoticism	3.14±2.90	2.64±2.80	n.s.
Sincerity	11.59±5.11	9.09±4.49	$p < 0.05$

Early-onset patients scored higher in interpersonal sensitivity ($p < 0.05$), hostility ($p < 0.05$), and psychoticism ($p < 0.05$) in the SCL-9 0, and in neuroticism ($p < 0.01$) and sincerity ($p < 0.05$) in the EPQ-A (Table 4).

4. Discussion

In our sample, the proportion of early-onset PD patients (10.2%) was slightly lower than that found in similar studies (26–28%) (Sheehan et al., 1981; Breier et al., 1984). These differences may be explained by our age threshold for 'early onset', fixed at 18 years, whereas it has been set at 20 years in other studies.

The finding of higher rates of PD in first-degree relatives confirms previous results (Goldstein et al., 1997; Battaglia et al., 1995) and suggests a greater genetic loading for early-onset PD. Goldstein et al. (1997) showed that these findings were not explained by current age of probands, phenomenology of panic disorder, comorbid major depressive disorder in probands, non-random mating, or length of

relatives' co-residence with symptomatic probands. Therefore, as has been suggested in relation to obsessive-compulsive disorder (OCD) (Bellodi et al., 1992) and mood disorders (Taylor and Abrams, 1973, 1981; Strober et al., 1988), PD patients with early onset may represent those cases with the greatest genetic loading. These data can be linked to the findings of Battaglia et al. (1998), who have recently reported the existence of anticipation phenomena in PD, i.e. the significant decrease in the time before the first episode of panic and onset of PD from the older to the younger generations. These authors claim that anticipation is a key for the genetics of PD and hypothesize a role for trinucleotide repeats sequences, concluding that this phenomenon may be considered to account for the familial aggregation of PD.

Our data are in accordance with reports of greater comorbidity with social phobia (Wittchen and Perkonigg, 1993) and alcoholism or other drug dependencies (Weissman et al., 1989). In contrast, our study does not support an association between early-onset PD and agoraphobia (Wittchen and Perkonigg, 1993; Goldstein et al., 1997), OCD (Goldstein et al., 1997) and affective disorders (Wittchen and Perkonigg, 1993). Since the samples from the Wittchen et al. and Goldstein et al. studies are smaller than ours, community-based epidemiological studies should be conducted to test these results.

Since social phobia and specific phobia (which show greater comorbidity with early-onset PD) are conditions beginning typically in childhood or adolescence (Marks and Gelder, 1986; Öst, 1987; Burke et al., 1990; Schneier et al., 1992; Magee et al., 1996; Kessler et al., 1998), it could be posited that early-onset PD is a special clinical subcategory with a distinct biological basis. Similarly, psychiatric symptoms begining in childhood and predisposing to adult disorders may be early manifestations of the same disorder or different manifestations of a common etiologic factor. A putative common pathogenic factor would be a temperamental dimension called 'behavioural inhibition', leading to school phobia and overanxious disorder in childhood and to several anxiety disorders in adulthood—such as social phobia and PD (Biederman et al., 1993; Rosenbaum et al., 1988, 1991a,b, 1993, 1994). These children appear to be introverted and socially inhibited, and respond to novelty with silence and isolation (Biederman et al., 1993; Rosenbaum et al., 1991a, 1993). In adulthood, they exhibit little assertiveness, low self-esteem and high interpersonal sensitivity (Rosenbaum et al., 1991b, 1994). These personality characteristics are consistent with the data about our sample's subjects, and have also been described in patients with comorbid PD and social phobia (Reiter et al., 1991). These features are characteristic of cluster C personality disorders (which include dependent, avoidant and obsessive-compulsive personality disorders), and are frequently associated with anxiety disorder (Alnaes and Torgersen, 1988; Reich et al., 1989; Schneier et al., 1991; Turner et al., 1991; Herbert et al., 1992). Neuroticism, which is related to these personality characteristics as well as to anxiety, was found to be higher in early-onset patients. Although this finding has the limitation of the small subsample's size, it is in accord with those of other studies (Kenardy et al., 1990) reporting that PD patients with an early age of onset displayed higher levels of neuroticism. To sum up, behavioural inhibition as a predisposing factor would account for the comorbidity between early-onset PD and other anxiety disorders (social phobia, simple phobia).

Early-onset PD patients were younger and had a longer clinical course. Although our study did not address the issue of treatment seeking, it could be speculated that, owing to their shyness, these patients waited for longer periods of time before seeking treatment. Such a finding would have significant clinical consequences. First, PD would appear to be ill-recognized during childhood and adolescence. Second, the existence of distinct subgroups of patients with early PD onset could therefore be hypothesized. Some patients with PD and social phobia would self-medicate using alcohol or other drugs, thus increasing their panic attacks. Another group of patients would develop earlier their PD in relation to abuse of alcohol or other drugs from early adolescence. Prospective follow-up studies should be conducted to test these hypotheses.

Early onset tends to be associated with increased clinical severity in major depressive disorder (Kovacs et al., 1988), bipolar disorder (Taylor and Abrams, 1981; Strober et al., 1988), and OCD (Minichiello et al., 1990). Goldstein et al. (1997) suggested that early-onset PD probands and first-

degree relatives may exhibit more clinical severity, but small sample size and lack of severity assessment scales are important limitations to their results. In our study, which overcame these two shortcomings, early-onset PD patients were not more likely to display more severe symptoms or worse social functioning. The recent report on PD anticipation by Battaglia et al. (1998) is in line with our results, as they found that the younger generations with an earlier PD onset did not have (as might be expected) greater clinical severity.

In a previous study, Wittchen and Perkonigg (1993) reported that early-onset PD patients were less likely to experience dyspnoea, smothering sensations and fear of dying. Goldstein et al. (1997) did not find differences in the probands' panic attacks symptoms, but a small sample of affected first-degree relatives more frequently reported derealization, choking feelings and faintness. These data seem to support our finding that early-onset PD patients were more likely to experience derealization/depersonalization feelings. Consistent with our results, Cassano et al. (1989); Toni et al. (1996) documented that PD with derealization/depersonalization symptoms had an earlier onset.

Two important limitations of our study should be considered: (a) Our results refer to two health centers in Barcelona (Spain) Seguí et al., 1998 and are not representative of the overall population with PD in our country. However, clinical and sociodemographic characteristics of the PD group were similar to those reported in other studies conducted in similar settings (Barlow et al., 1985; Aronson and Logue, 1988; Noyes et al., 1987; Rapee et al., 1990; Starcevic et al., 1993; Cox et al., 1994). Also, the comorbidity rate is similar to that reported by other authors (Magee et al., 1996). (b) Another limitation to our study is that family history could not be assessed through direct interview. However, our results are in accord with Goldstein et al. (1997), the only research employing this kind of methodology.

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