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Parental Antecedents of Psychosis Are Associated With Severity of Positive and Negative Symptoms in Schizophrenia Patients

To the Editor: Heritability in liability to schizophrenia has been estimated at 81%.¹ Therefore, genetic risk factors play a key role in the complex etiology of schizophrenia, and they are also thought to affect the presentation of schizophrenia symptoms. Consequently, the severity of symptoms should be greater among schizophrenia patients with familial antecedents of psychoses than for nonfamilial or sporadic cases. However, few studies have compared the symptoms of familial and nonfamilial schizophrenia, and those that have investigated only small samples.²⁻⁴ We compared the symptom severity of patients who had a parent with a diagnosis of schizophrenia to that of patients with no antecedent of either psychotic or affective disorder among their parents or grandparents.

Method. The participants were 211 patients with a diagnosis of schizophrenia according to *DSM-IV* criteria who had 1 first-degree relative willing to cooperate in the collection of the patient's familial psychiatric antecedents. Antecedents were assessed using the Family History Research Diagnostic Criteria (FH-RDC),⁵ as previously described,⁶ and symptom severity was assessed using the Spanish adaptation of the Positive and Negative Syndrome Scale (PANSS).^{7,8} We used the classical PANSS subscales described by

Kay et al,⁷ and we also grouped symptoms using the 5-factor model suggested by Wallwork et al.⁹ We identified 39 (18.5%) familial patients, defined by the presence of 1 parent with schizophrenia (10 fathers and 29 mothers), and 172 (81.5%) sporadic patients, who had no psychotic antecedent among their parents or grandparents. All participants were clinically stable white outpatients, without prominent psychotic symptoms (mean ± SD positive and negative PANSS scores of 12.9 ± 6.2 and 17.7 ± 7.7, respectively), and they were able to understand the purpose of the study. Informed consent was obtained from both the patients and their relatives, and the investigation was approved by the Ethics Committee of the Hospital Sant Joan de Reus. The general linear model was used to compare the PANSS scores of patients with and without parental antecedents of schizophrenia, with current age as a covariate. Estimated marginal means were calculated instead of average means to adjust the PANSS scores to the current age. The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp, Armonk, NY).

Results. Table 1 shows the sample characteristics and the results of the study. Patients with parental antecedents of schizophrenia presented higher estimated marginal means on all of the PANSS subscales, and statistically significant differences were observed in the positive and negative subscales described by Kay et al⁷ and in the negative and disorganized subscales described by Wallwork et al.⁹

Table 1. Sample Characteristics and General Linear Model Analyses Comparing the PANSS Subscale Scores of Schizophrenia Patients Depending on the Presence of Parental Antecedents of Psychosis

Sample Characteristic	Patients Without Parental Antecedents of Psychosis (n = 172)		Patients With Parental Antecedents of Psychosis (n = 39)		Statistical Test	P			
	EMM (SE)	95% CI	EMM ± SE	95% CI			F	P	Partial η ²
Age, mean (SD), y	33.2 (11.7)		39.7 (15.2)		t = 2.515	.015			
Gender, n (%)					χ ² = 0.379	.538			
Male	119 (69.2)		25 (64.1)						
Female	53 (30.8)		14 (35.9)						
Age at first psychiatric contact, mean (SD), y	22.2 (5.5)		22.3 (7.1)		t = 0.059	.953			
Age at first psychiatric admission, mean (SD), y	23.8 (6.1)		25.4 (7.6)		t = 1.338	.183			
Age at onset, mean (SD), y	22.0 (5.5)		21.3 (4.9)		t = 0.741	.460			
Substance consumption, n (%)					χ ² = 1.043	.307			
Amphetamines	17 (9.9)		2 (5.1)						
Cocaine	30 (17.4)		5 (12.8)		χ ² = 0.542	.462			
Opiates	4 (2.3)		2 (5.1)		χ ² = 0.753	.386			
Hallucinogens	8 (4.7)		2 (5.1)		χ ² = 0.012	.914			
Cannabis	68 (39.5)		14 (35.9)		χ ² = 0.240	.632			
Alcohol	91 (52.9)		22 (56.4)		χ ² = 0.106	.745			
Cigarettes	108 (62.8)		23 (59.0)		χ ² = 0.325	.569			
General linear model^a									
PANSS component	EMM (SE)	95% CI	EMM ± SE	95% CI	F	P	Partial η ²	Observed Power	
Kay et al ⁷									
Positive	12.4 ± 0.5	11.5–13.3	14.8 ± 1.0	12.9–16.7	4.797	.030	0.023	0.587	
Negative	16.9 ± 0.5	15.9–18.0	21.3 ± 1.1	19.1–23.5	12.532	<.001	0.057	0.941	
General	28.4 ± 0.7	27.0–29.9	29.7 ± 1.6	26.6–32.7	0.512	.475	0.002	0.110	
Wallwork et al ⁹									
Positive	7.4 ± 0.3	6.8–8.0	8.7 ± 0.7	7.4–10.0	3.063	.082	0.015	0.414	
Negative	14.1 ± 0.4	13.2–14.9	17.2 ± 0.9	15.4–19.0	9.301	.003	0.043	0.859	
Disorganized	6.2 ± 0.2	5.8–6.6	7.3 ± 0.5	6.4–8.2	4.481	.035	0.021	0.558	
Excited	6.1 ± 0.2	5.7–6.4	6.2 ± 0.4	5.4–7.1	0.179	.672	0.001	0.071	
Depressed	5.5 ± 0.2	5.1–5.8	5.8 ± 0.4	5.0–6.6	0.431	.512	0.002	0.100	
Total PANSS score	57.8 ± 1.4	55.1–60.5	65.6 ± 2.9	59.9–71.4	5.842	.017	0.027	0.672	

^aPatients with a family history of psychosis were significantly older; therefore, the data were analyzed using the general linear model, which included current age as a covariate. Similar results were obtained irrespective of whether we considered years of disease evolution or current age in the general linear model. Boldface indicates statistical significance.

Abbreviations: CI = confidence interval, EMM = estimated marginal mean, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation, SE = standard error.

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The present study found that patients with parental antecedents of schizophrenia presented a more severe phenotype, as measured by the positive and negative PANSS subscales. Patients with antecedents of psychoses in parents presented a more severe phenotype, according to the positive and negative subscales of Kay et al⁷ and the negative and disorganized dimensions of Wallwork et al.⁹ Although we were not able to consider the environmental effect of being brought up by a parent with schizophrenia, epidemiologic studies have shown greater effects for genetic factors than for environmental factors.¹ Previous studies comparing the symptomatology of familial and nonfamilial cases have associated familial schizophrenia with greater severity of both negative^{2,3} and positive symptoms,⁴ though not in the same study. Familial schizophrenia has also been associated with an earlier age at onset, more severe structural brain abnormalities, a higher number of minor physical anomalies, a higher incidence of deficit syndrome, poorer outcomes, and greater impairment of cognitive functions.¹⁰ Historically, having a first-degree relative diagnosed with schizophrenia has been identified as the main risk factor for developing the illness, with an odds ratio of 9.8.¹ Similar results have recently been found by large population-based studies.^{11,12} Interestingly, Agerbo et al¹¹ showed that the risk of schizophrenia among individuals with a first-degree relative with the disease was 8.3, similar to the 8.0 value suggested by the Polygenic Risk Score (PRS), a composite score based on associated genetic variants. Agerbo et al noted a significant interaction between the PRS and family history of schizophrenia, which seems to indicate that patients with familial antecedents present higher genetic liability.

The results of the present study emphasize the need to consider the antecedents of psychosis in clinical practice, because having a family history of schizophrenia is associated with a more severe clinical expression of the disease. Additionally, our results contribute new evidence that the stratification of the sample according to the presence of psychosis in the family may reduce the heterogeneity of schizophrenia and could be a valuable variable in clinical and genetic studies intending to elucidate the neurobiological basis of schizophrenia.

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