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The child and adolescent first-episode psychosis study (CAFEPS): Design and baseline results ☆

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Abstract

Objective: The child and adolescent first-episode psychosis study (CAFEPS) is a multicenter, two-year, longitudinal project aiming to evaluate different clinical, neuropsychological, neuroimaging, biochemical, immunological, and genetic variables and treatment and prognostic factors in these patients. This paper describes the methods and rationale behind the study and the general characteristics of the sample.
Method: At six different centers, from March 2003 through November 2005, we consecutively recruited 110 patients, ages 9–17 years, who presented with a first psychotic episode. Controls were recruited from the same geographic areas and were matched for gender and age.
Results: Patients had lower socioeconomic status (SES) ($p=0.018$) and parental years of education ($p<0.001$) than controls. The percentage of patients recruited increased with age ($p<0.001$) and there was a higher percentage of males ($p<0.001$). The total mean PANSS score was 89.03±20.1, the positive score 23.8±6.5 and the negative score 20.02±8.8. There were no significant differences

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between the genders with respect to age, parental years of education, SES, or scores in premorbid adjustment or general functioning. There were statistically significant positive correlations between age and positive symptoms and between all PANSS subscales and the Disability Assessment Schedule, and negative correlations between positive symptoms and global functioning. Diagnoses after the baseline evaluation were: psychotic disorder not otherwise specified (NOS) 35.5%, schizophreniform disorder 24.5%, mood disorder with psychotic symptoms 22.7%, schizophrenia 10%, schizoaffective disorder 2.7%, and other psychotic disorders 4.5%. Patients had worse premorbid adjustment ($p<0.001$) and global functioning ($p<0.001$) than controls after controlling for SES.
Conclusions: Infancy and adolescence adjustment and global functioning are lower in children and adolescents with psychotic disorders than in controls, severity of symptoms are related to general disability, and the most frequent diagnoses are psychotic disorders NOS.

Keywords: Child-onset; First-episode psychoses; Early-onset; Children; Adolescents

1. Introduction

Psychotic disorders often begin during childhood and adolescence and their negative impact on normal development and functioning can be devastating (Volkmar, 1996). Psychosis with a very early age of onset may have a more severe presentation than the adult-onset form. Although there is evidence that childhood-onset psychotic disorders bear many similarities to adult-onset psychotic disorders and can be diagnosed using similar criteria, child- and adolescent-onset first-episode psychosis needs to be further studied in order to identify its specific features, differential diagnosis, treatment of choice, and outcome (Asarnow et al., 2004; Ballageer et al., 2005). Psychiatrists need to become familiar with the specific characteristics of childhood-onset psychosis in order to make adequate differential diagnoses and devise treatment plans. Several studies have tried to describe first psychotic episodes in children and adolescents (Werry et al., 1994; McKenna et al., 1994; Spencer and Campbell, 1994; McClellan et al., 2002), but diagnosis can be difficult. Firstly, it can be difficult to distinguish between immature responses such as the magical thinking often present in young children and real symptoms such as delusions. Secondly, childhood-onset psychosis is frequently insidious, with the emergence of smaller-scale problems prior to the presence of full-blown psychotic symptoms. Thirdly, a high percentage of childhood- and adolescent-onset prodromal psychotic symptoms (Correll et al., 2005) or overt psychoses (Menezes and Milovan, 2000) have been associated with a diagnosis other than schizophrenia at follow-up, with a presentation similar to that of other conditions such as bipolar or depressive disorders, thus making it difficult to reach an accurate diagnosis at the time of onset of symptoms.

Childhood-onset psychoses have several advantages in terms of studying the pathophysiology of the disease, such as a potentially more homogeneous population with a possibly greater genetic load and the better match for years of education, since patients and controls still attend compulsory school. However, very few longitudinal first-episode early-onset studies have been published. Most of those available were produced by the same group at the NIMH and the patients enrolled had a mean duration of illness of 3 years prior to the first assessment (Nicolson and Rapoport, 1999; Nicolson et al., 2000). The other available longitudinal studies include small samples or focus only on specific assessments (Werry et al., 1994; McKenna et al., 1994; Spencer and Campbell, 1994; McClellan et al., 2002). Though our understanding of childhood-onset psychosis has increased in recent years, there continues to be a strong need for data on differential diagnosis, comorbidity, and neurobiological and genetic factors, as well as treatment and prognosis (Kumra et al., 2002; Asarnow et al., 2004). The child and adolescent first-episode psychosis study (CAFEPS) is a multicenter, longitudinal, follow-up study, designed to evaluate clinical, neuropsychological, neuroimaging, biochemical, immunological, and genetic variables in early-onset first psychotic episode patients in Spain. Our goal was to assess clinical characteristics, prognostic factors, diagnostic specificities of findings, and pathophysiological changes in the brain during the first 2 years after the psychotic episode through an integrative and translational approach. This article describes the procedure and assessment instruments used, and presents the baseline demographic and general clinical characteristics of the sample.

2. Subjects and methods

2.1. Subjects

The CAFEPS sample included 110 children and adolescents ages 9 through 17 years with a diagnosis of

Table 1
Institutions of enrollment of patients and controls

	Patients		Controls	
Clinical institution	N	%	N	%
Hospital Universitario Gregorio Marañon, Madrid	42	38.2	43	44.9
Hospital Clínic Universitari, Barcelona	28	25.5	28	28.6
Hospital Santiago Apóstol, Vitoria	15	13.6	8	8.1
Hospital Niño Jesús, Madrid	11	10.0	3	3.1
Hospital Universitario Marqués de Valdecilla and Center of Child and Adolescent Mental Health, Cantabria	8	7.3	11	11.2
Clínica Universitaria, University of Navarra	6	5.5	5	5.1
Total	110	100	98	100

a first psychotic episode, and 98 matched healthy control subjects. Patients were recruited from child and adolescent psychiatry units at six university hospitals with experience in performing and assessing diagnoses, and evaluation and treatment with semi-structured interviews and clinical scales. The six hospitals were located in Madrid, Barcelona, Vitoria, Santander, and Pamplona, covering a population of approximately 8 million people. All patients attended at these facilities during the recruitment period who met the inclusion criteria described below were invited to participate in the study.

2.1.1. Recruitment

Patients: Table 1 shows the institutions where patients and controls were enrolled. The recruitment period was from March 2003 through November 2005. The inclusion criteria for patients were: age between 7 and 17 years at the time of first evaluation and presence of positive psychotic symptoms (within a psychotic episode) such as delusions or hallucinations of less than 6 months' duration. This short duration of positive psychotic symptoms was established in order to obtain a more homogeneous sample and to avoid the influence of variables such as years of psychopharmacological treatment or institutionalization. Other positive symptoms such as disorganized speech or behavior were not included due to the difficulty in assessing those and their time course, retrospectively. Exclusion criteria were: presence of a concomitant Axis I disorder at the time of evaluation that might account for the psychotic symptoms (such as substance abuse, autistic spectrum disorders, post-traumatic stress disorder, or acute stress disorder), mental retardation (MR) per the DSM-IV criteria, including not only an IQ below 70 but also impaired functioning, pervasive developmental disorder, neurological disorders, history of head trauma with loss of consciousness, and pregnancy. Occasional substance use was not an exclusion criterion if positive symptoms persisted for more than 2 weeks after a negative urine drug test. During the recruitment period, 116 patients met the inclusion criteria. However, 6 patients were excluded, 3 due to MR and 3 due to parental refusal to consent.

Controls: We selected healthy controls from publicly-funded schools with characteristics similar to those attended by patients in the community through advertisements and from children who were seen for routine pediatric visits at our hospitals, all from the same geographic areas. Controls were offered a coupon to buy school supplies in compensation for their participation and a trained psychologist conducted a preliminary telephone screening to check for exclusion criteria. Those who passed the initial screening were interviewed with their relatives at the clinical centers by experienced child and adolescent psychiatrists. The inclusion criteria for controls were similar age and sex as patients, coming from the same geographical areas as patients, no psychiatric disorder as measured by the Kiddie-SADS-Present and Lifetime Version (K-SADS), and no neurological disorders, head trauma, pregnancy, or MR (again per DSM-IV criteria). Six controls were excluded due to diagnosis of a psychiatric disorder after the first evaluation (2 attention deficit–hyperactivity disorder, 3 anxiety disorder, 1 anorexia nervosa).

2.2. Procedure

Diagnosis was made according to the DSM-IV criteria (American Psychiatric Association, 1994) using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997). The K-SADS-PL was administered individually to parents and children in separate interviews by experienced child psychiatrists with specific training in the semi-structured interview. SES was estimated with the Hollingshead Redlich scale (Hollingshead and Redlich, 1958) administered by the clinician to the parents. Parental years of education were recorded as well as psychiatric disorders in first- and second-degree relatives. At baseline, a complete evaluation (structured interview, clinical scales, family environment, prognostic and premorbid adjustment scales, neuropsychological assessment, neuroimaging, genetic, immunological, and oxidative stress determinations) was performed. The psychopharmacological treatment and side effects were also recorded. Clinical, functional, and disability scales were again administered at 6 months, and 1 and 2 years. The UKU Side Effect Rating Scale was administered at

baseline, after 8 weeks, 6 months, and 1 and 2 years. At the two-year follow-up visit, apart from the clinical and side effect scales, the structured diagnostic interview (K-SADS), the neuropsychological assessment, and the neuroimaging and the oxidative stress evaluations were repeated. In control subjects, a complete evaluation with the same battery of interviews, scales, neuroimaging and neuropsychological assessment, genetic, immunological, and oxidative stress determinations was performed at baseline and after 2 years. Patients who developed any psychiatric disorder during this period were not excluded from the initial analysis but were excluded from the final comparisons. In order to control for center-specific effects, meetings of all clinicians were held to analyze the inter-rater reliability of different scales and to discuss any doubts about the inclusion criteria or evaluation of patients.

2.2.1. Diagnostic interview

The K-SADS-PL (Kaufman et al., 1997) is a semi-structured diagnostic interview designed to assess current and past psychopathology in children and adolescents according to DSM-IV criteria (American Psychiatric Association, 1994). We used the Spanish translation of the K-SADS-PL (De la Peña et al., 2002; Ulloa et al., 2006).

2.2.2. Assessment scales

We used scales originally designed for use in adult samples in order to study adolescents longitudinally, with these assessments as baseline comparisons. The scales used were the following:

The Lewis–Murray Scale of Obstetric Data (Lewis et al., 1989). This is a scale administered by the clinician that retrospectively rates information on obstetric complications from pregnancy and birth medical records and maternal interviews. It was derived from a consensus of six previous scales and consists of 15 complications with thresholds for rating them as "definite" or "equivocal."

The Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987). We used the validated Spanish version of the PANSS (Peralta and Cuesta, 1994) to assess psychopathological symptoms of schizophrenia. It comprises a total scale score of 30 items and 3 subscales (positive symptoms, negative symptoms, and general psychopathology). The reliability of the different clinicians administering the scale was evaluated and within-class correlation coefficients were higher than 0.8.

The Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967), a 17-item scale administered by the clinician to patients in order to evaluate the severity of depressive symptoms during the previous week.

The Young Mania Rating Scale (YMRS) (Young et al., 1978), an 11-item scale developed to evaluate the severity of symptoms of mania. It was also scored by the clinician based on information provided by the patients.

The abbreviated version of the Scale to Assess Unawareness of Mental Disorder (SUMD) (Amador et al., 1993). This scale has 3 general items on awareness of the disease, awareness of its social consequences, and the need for treatment. It also rates awareness and attribution of six symptoms. It was completed by the clinician with information provided by the patients.

The Clinical Global Impression Scale (CGI) (Guy and ECDEU, 1976), which assesses severity and improvement of global symptomatology on a scale of 1 to 7. It was completed by the clinician.

The Global Assessment of Functioning Scale (GAF) (Endicott et al., 1976), which measures the severity of symptoms and the level of functioning on a scale from 1 to 100, evaluated by the clinician with the patient.

The Strauss–Carpenter Outcomes Scale (SCOS) (Strauss and Carpenter, 1972), which includes four dimensions: degree of meaningful occupation, degree of social contacts, degree of psychotic symptoms, and number of days of inpatient treatment during the previous year. The total score on the scale has good prognostic value and a high correlation with outcome criteria in schizophrenic patients. It is also administered by the clinician with the information provided by the patients and parents.

The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982), a measure of premorbid functioning. The areas explored are sociability and withdrawal, peer relationships, school achievement, adaptation to school, and ability to establish socio-affective and sexual relationships. The scale considers different age ranges: childhood (up to 11 years), early adolescence (12 to 15 years), late adolescence (16 to 18 years), and adulthood (19 years and older). Each item is scored from 0 to 6, with 0 indicating the best level of adjustment. This scale was completed by the clinician based on information obtained from the patient and parents.

The Neurological Examination Scale (NES) (Buchanan and Heinrichs, 1989) was used to assess neurological "soft signs." It comprises 26 items clustered in 4 subscales: sensory integration, motor coordination, sequencing of complex motor tasks, and other neurological soft signs. For the present study, reliability was determined for the clinicians from the different clinical settings, and the within-class correlation coefficients ranged from 0.80 to 0.99 in the total and all subscale scores.

The Family Environment Scale (FES) (Moos and Moos, 1986), a 90-item self-report scale which includes

10 subscales reflecting socio-environmental characteristics of the families.

The Parent–Adolescent Communication Inventory (PACI) (Barnes and Olson, 1992), a 20-item self-report scale assessing openness, selectivity, strengths, weaknesses, and problematic issues in the adolescent–mother and adolescent–father dyads.

The Strengths and Difficulties Questionnaire (SDQ) (Goodman, 2001), a behavioral questionnaire for children and adolescents ages 4 to 17. It is a valid and reliable instrument with five subscales of emotional symptoms, conduct problems, hyperactive behavior, peer relationships, and prosocial behavior. Three versions (parents, children, and teachers) were used and, therefore, three informants completed the questionnaires.

The World Health Organization Disability Assessment Schedule (WHO-DAS) short version (Janca et al., 1996). This instrument assesses difficulties in maintaining personal care, performing occupational tasks, and functioning in family and social settings. It is administered by the clinician.

The Scale of the Udvalg for Kiniske Undersogelser (Committee of Clinical Trials), UKU (Lingjaerde et al., 1987), a comprehensive rating scale administered by the clinician to assess general side effects of psychotropic drugs.

2.2.3. Neuropsychological tests

Different studies point out that patients with early-onset psychosis present cognitive impairment in attention and information processing (Kenny et al., 1997), learning and memory (McClellan et al., 2004), working memory (Kravariti et al., 2003), and executive functioning (Kumra et al., 2000). These cognitive deficits have been reported to be already present at the time of illness onset (Brickman et al., 2004a,b). The neuropsychological battery employed in this study was designed to address these four cognitive domains, by means of standardized neuropsychological tests that have proven sensibility and specificity to these cognitive domains (Lezak, 1995) and that have been previously used in the cognitive assessment of this type of patient.

Neuropsychological assessment in children and adolescent must take into account their different developmental levels. In order to estimate global functioning in the form of IQ, vocabulary and cubes of the WISC-R or WAIS-III were used for patients and controls under and over 16 years of age, respectively. The potentially impaired cognitive domains were assessed with the following instruments: attention by means of the Conners′ Continuous Performance Test-II (Conners, 2000), digit span, Stroop words, Stroop colors, trail making test part A, memory (by means of the Spanish version of the California Verbal Learning Test), working memory (digits backwards, letter and number sequencing, trial making test part B, and executive functioning (by means of the Wisconsin Card Sorting Test, Stroop color–word interference test, and verbal fluency).

2.2.4. Neuroimaging assessment

Magnetic resonance imaging (MRI) data were obtained from five different scanning facilities, two with a Siemens Symphony, two with a General Electric Sigma, and one with a Philips Gyroscan. Two MRI sequences were acquired for each subject, a T1-weighted 3D gradient echo sequence (matrix size 256×256, voxel size $1 \times 1 \times 1.5$ mm) and a T2-weighted turbo-spin echo sequence (turbo factor 15, echo time 120 ms, matrix size 256×256, voxel size $1 \times 1 \times 3.5$ mm). To obtain volume measurements of the main brain lobes, we used a method for semi-automated segmentation of the brain based on the Talairach proportional grid system, similar to those described in Kates et al. (1999). First, brain tissues were segmented into gray matter, white matter, and cerebrospinal fluid based on the intracranial volume of the T1-weighted image, using an automated method included in the SPM2 (Statistical Parametric Mapping) program (Ashburner and Friston, 1997). In a second stage, we applied the Talairach reference system (Talairach and Tournoux, 1988) to define regions of interest (ROIs) and to obtain volume data. Magnetic resonance images were processed using locally developed software that incorporates a variety of image processing and quantification tools (Desco et al., 2001). This methodological procedure has been used and validated in several previous studies (Molina et al., 2005; Moreno et al., 2005). The magnetic resonance spectroscopy protocol consisted of a single-voxel PRESS technique (TR/TE 1500/136 ms and 128 acquisitions) acquiring a boxcar-shaped voxel ($3.0 \times 1.5 \times 1.5$ cc) placed in the right and left dorsolateral prefrontal (DLPF) regions. The voxel was initially placed anterior to the middle frontal gyrus in axial orientation and then rotated (yaw, pitch, and roll) to maximize its gray matter content. This protocol was followed in both hemispheres. Two spectra were acquired from each localization, with and without water suppression, respectively. The water spectrum was acquired to establish a reference signal for normalization of the metabolite signal. In the water-suppressed spectra, the residual water was removed using an HSVD method (Boogaart, 1994). Signal quantification was performed using a non-linear time

domain analysis procedure (AMARES) (Vanhamme et al., 1997). Normalized values were obtained by dividing the intensity of each peak by the water signal. NAA and Cho values were expressed as ratios to Cr. The problems arising from the use of different scanner machines were discussed in a previous report (Reig et al., 2005).

2.2.5. Immunological evaluation

Immunological dysfunction at different levels of the immune system has been implicated in the pathophysiology of schizophrenia (Ganguli et al., 1987). Patients with psychosis may have impaired production of Th1 cytokines and over-activation of the Th2 system, leading to a dysfunction in the normal Th1/Th2 balance (Müller et al., 2000). Recent investigations seem to point to over-activation of Th1 activity and, therefore, a higher Th1/Th2 cytokine ratio in schizophrenia (Kim et al., 2004). This immunological dysfunction may promote an autoimmune reaction that may contribute to the psychotic state (Noy et al., 1994). However, the existence of immunological anomalies in early-onset psychosis and their feasible clinical impact have not been investigated. The aims of the present study, in a sample of antipsychotic–naïve early-onset psychosis patients, were (1) to assess serum cytokine concentration during the acute phase of the illness and, after 6 weeks of treatment, (2) to explore whether these cytokine levels are related to changes in the severity of symptomatology. Our aim was to evaluate plasma levels of cytokines (Th1 and Th2) during the acute phase of the illness and their association with clinical features. To do so, fasting venous blood (10 ml) was drawn in a sodium citrate vacuum tube from each patient and healthy volunteer between 8:00 am and 10:00 am. The patient blood sample was obtained within 72 h of the initial administration of an antipsychotic to preclude possible effects of mediation at the baseline assessment. The blood was immediately processed as follows: tubes were centrifuged for 5 min at 400 g at 4 °C. The plasma was collected and centrifuged for 15 min at 14,000 g at 4 °C and then stored in 10% glycerol at −85 °C until thawed for assay. Blood was sampled at baseline, for patients and controls, and also 6 weeks later for patients. Thus, the level of IL-12 p70 was measured by quantitative "sandwich" enzyme-linked immunosorbent assay (ELISA) with a commercially available kit (Biosource Europe). According to the manufacturer's instructions, these kits are suitable for serum, plasma, tissue cultures, and buffered solutions.

2.2.6. Oxidative stress evaluation

According to some authors, there is now substantial evidence that oxidative stress and oxidative cell damage exist in schizophrenia (Mahadik and Mukherjee, 1996; Zhang et al., 2006). These previous studies include the primary antioxidant defense, i.e. the enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), and also glutathione (GSH), the main non-protein antioxidant. GSH is an important redox regulator, and its deficit could be responsible for cortical anomalies, particularly in regions rich in dopamine innervation (Do et al., 2000). On the other hand, increased levels of lipid peroxides have been the most frequently used index of oxidative cell damage. Since oxidative stress is systemic, peripheral measures have been found to be relevant for the assessment of oxidative brain cell damage (Mukherjee et al., 1996; Zhang et al., 2006). The study of these markers in first-episode psychotic patients and their evolution with chronic antipsychotic treatment may provide new insights into progression of the disease from childhood and adolescence; it might show how these variables predate the illness and how antipsychotic treatments may alter it. Blood samples were processed following standard procedures; blood cells and serum were immediately frozen at −80 °C until analysis. Oxidative stress was evaluated by measuring primary enzymatic antioxidant defense (cellular glutathione peroxidase, catalase, and superoxide dismutase activities) and plasma levels of antioxidants, glutathione, and lipid peroxidation. Oxidative stress markers were determined by standardized spectrophotometric determinations (Bioxytech, CA, USA) in a diode-array spectrophotometer (Beckman, CA, USA).

2.2.7. Genetic test. genotype determination

There is evidence of alterations in the expression of serotonin (5-HT) receptors and transporters observed in the brains of patients with schizophrenia and other psychiatric disorders (Pralong et al., 2000). These alterations may originate at the DNA level due to sequence mutations that alter the functioning of serotonin receptors and transporters. We analyzed polymorphisms-1438 A/G, T102C and H452T (5-HT2A), C23S (5-HT2C) and HTTLPR and VNTRi2 of the 5-HTT gene (serotonin transporter). The Catechol-*O*-methyltransferase (COMT) gene has been proposed as a candidate for the genetic component in schizophrenia and it has recently been pointed out as probably the only gene for which a causal allele (Val at Val158Met) and a mechanism that predisposes to schizophrenia have been identified. In addition, it has recently been published that the Val158Met polymorphism correlates with several neuropsychological markers of interest (Harrison and Weinberger, 2005). The polymorphisms in the dopamine receptor genes were included, given the evidence of the

involvement of the dopaminergic system in the etiology and symptoms of schizophrenia (Staddon et al., 2005). The C677T polymorphism of the MTHFR gene was added as its role in the development of schizophrenia has been also suggested (Lewis et al., 2005; Muntjewerff et al., 2006). For the present study, DNA was extracted from peripheral blood anticoagulated in EDTA or from a buccal swab following standard procedures. The following polymorphisms were analyzed by means of PCR-RFLP (Polymerase Chain Reaction coupled with Restriction Fragment Length Polymorphisms): V158M (COMT gene), C677T (methylenetetrahydrofolate gene, MTHFR), Taq I (dopamine receptor 2, DRD2), S9G (dopamine receptor 3, DRD3),-1438 A/G, T102C and H452T (5-HT2A) and C23S (5-HT2C). The resulting fragments were scored in agarose gels and samples were genotyped accordingly. For HTTLPR and VNTRi2 polymorphisms of the 5-HTT gene (serotonin transporter), the alleles were resolved in high-resolution polyacrylamide gels for genotyping.

2.3. Ethical issues

The study was approved by the IRBs of all participating clinical centers. All parents or legal guardians gave written informed consent before the study and patients agreed to participate. The genetic part of the study had a specific informed consent form. Since this was a naturalistic study, there were no guidelines for the treatment administered (drugs, psychotherapy, and so on).

2.4. Data analyses

Statistical analyses were carried out with SPSS v11.0 (Statistical Package for the Social Sciences, Chicago, USA) and differences of $p<0.05$ were considered significant. For descriptive purposes, the continuous variables were expressed as means, standard deviations (SD) and ranges, and frequencies and/or percentages were used to describe the categorical variables. The chi square test (χ^2) was used to compare percentages of discrete variables. Student's t test for independent samples was used to compare means for continuous variables. Kolmogorov–Smirnov tests were conducted to assess the normality of continuous and ordinal variables. When abnormal, non-parametric tests (Mann–Whitney U) were used. The Spearman non-parametric correlation was used to determine the association between continuous variables. For multiple comparisons a Multiple Analysis of Variance (MANOVA) was used, and in some cases with some variables as covariates (MANCOVA), with the Bonferroni test to adjust for multiple comparisons.

Table 2
Distribution of patients and controls by age, socioeconomic status, sex, and race

	Controls (N=98)	Patients (N=110)
	N (%)	N (%)
Age (years) (χ^2=7.7; p=0.463)		
9	2 (2.0%)	1 (0.9%)
10	2 (2.0%)	0 (0%)
11	2 (2.0%)	4 (3.6%)
12	3 (3.1%)	4 (3.6%)
13	8 (8.2%)	4 (3.6%)
14	10 (10.2%)	13 (11.8%)
15	19 (19.4%)	17 (15.5%)
16	22 (22.4%)	21 (19.1%)
17	30 (30.6%)	46 (41.8%)
Socioeconomic status (χ^2=11.9; p=0.018)		
5 (lowest)	11 (11.2%)	24 (21.8%)
4	23 (13.5%)	36 (32.7%)
3	26 (26.5%)	24 (21.8%)
2	10 (10.2%)	12 (10.9%)
1 (highest)	28 (28.6%)	14 (12.7%)
Gender (χ^2=0.57; p=0.448)		
Males	61 (62.2%)	74 (67.3%)
Race (χ^2=4.2; p=0.125)		
Caucasian	91 (92.8%)	94 (85.5%)
Hispanic	5 (5.4%)	7 (6.4%)
Others	2 (2.0%)	9 (8.1%)

3. Results

3.1. Sociodemographic characteristics of the sample

Age, SES, sex, and race distribution for patients and controls are shown in Table 2. Mean age was similar (patients 15.5±1.8 and controls 15.2±1.9) (Mann–Whitney U test: Z=1.5; p=0.130). The percentage of patients recruited increased with age (χ^2=112.8; $p<0.001$) and males were over-represented (χ^2=13.1; $p<0.001$) in this first-episode cohort. SES differed significantly between patients and controls, but age, sex, and race distributions did not. Mean parental years of education was significantly higher for the control group (14.2±4.8) than for patients (10.8±4.9) (t=5.1; $p<0.001$).

The mean age of male (15.7±1.8) and female (15.2±1.8) patients was similar (Mann–Whitney U Test: Z=1.4; p=0.161) as was the mean of male (10.7±5.1) and female (10.9±4.7) parental years of education (t=0.3; p=0.759). Distribution of SES did not differ significantly between the genders (χ^2=2.4; p=0.665). Moreover, there were not any global differences between male and female patients in PAS,

Table 3
Correlations (Spearman's rho) between severity and duration of symptoms and age and premorbid and general function scales in patients

	Age	PAS	GAF	DAS
PANSS				
Positive symptoms	0.30**	0.11	−0.30**	0.24*
Negative symptoms	−0.11	0.19*	0.19	0.35***
General symptoms	0.08	0.08	−0.03	0.35***
Total symptoms	0.08	0.19*	−0.06	0.42***

*$p<0.05$; **$p<0.01$; ***$p<0.001$.

DAS, and GAF scores (MANOVA: $F=2.5$; $df=106$; $p=0.061$; effect size=0.067).

3.2. Clinical characteristics of psychotic patients and psychopharmacological treatment

At the time of first assessment, 92 (83.6%) patients were hospitalized in a child psychiatric department and 18 (16.4%) were in outpatient treatment. The mean duration of positive symptoms was 2.1±1.7 months (range: 1 to 6 months), negative symptoms 5.2±7.1 months (range: 1 to 35 months), and affective symptoms 6.9±16.1 months (range: 1 week to 117 months). On the PANSS, the mean total score was 89.0±20.1 (range: 30 to 146), the mean positive scale score 23.8±6.5 (range: 7 to 45), the mean negative scale score 20.0±8.8 (range: 7 to 42), and the mean general scale score 45.0±10.6 (range: 16 to 74). Fifty-six (50.9%) patients were already receiving psychopharmacological treatment at the time of enrollment. The main psychopharmacological treatments prior to enrollment in the study were second generation antipsychotics ($N=38$; 34.5%), first generation antipsychotics ($N=4$;3.6%), antidepressants ($N=9$; 8.2%), methylphenidate ($N=2$; 1.8%), and benzodiazepines ($N=3$; 2.7%).

Table 4
Diagnostic spectra at baseline ($N=110$)

Diagnosis	*N* (%)
Psychotic disorder not otherwise specified	39 (35.5%)
Schizophreniform disorder	27 (24.5%)
Depressive disorder with psychotic symptoms	13 (11.8%)
Bipolar disorder, manic episode with psychotic symptoms	12 (10.9%)
Schizophrenia	11 (10%)
Schizoaffective disorder	5 (4.5%)
Other psychotic disorders	3 (2.7%)

Table 5
Differences between patients ($N=110$) and controls (98) on premorbid adjustment, disability, and global functioning scales

	Patients	Controls	F^{a}_{df}	*p*	Effect size
	Mean (SD)	Mean (SD)			
Premorbid Adjustment Scale (PAS)	42.9 (20.8)	11.0 (7.6)	140.1_{197}	<0.001	0.416
Disability Assessment Scale (DAS)	11.4 (4.2)	0.7 (1.5)	366.1_{197}	<0.001	0.650
Global Assessment Functioning Scale (GAF)	33.5 (14.8)	91.7 (5.0)	783.6_{197}	<0.001	0.799

[a]Multiple analysis of variance with socioeconomic status and parental years of education as covariants (MANCOVA).

3.3. Correlations between severity and duration of symptoms and function scales

Correlations between PANSS subscales with age and premorbid and functioning scales are shown in Table 3. There were statistically significant positive correlations between age and PANSS positive symptoms and between all PANSS subscales and the DAS. A negative correlation was found between PANSS positive symptoms and the GAF. A low but positive correlation was found between negative symptoms and total PANSS score and worse premorbid adjustment.

3.4. Diagnoses at baseline evaluation

Diagnoses at the baseline evaluation are shown in Table 4. The most common diagnoses at the first evaluation were psychotic disorder NOS and schizophreniform disorder. A substantial percentage of patients were diagnosed with depressive or manic episodes with psychotic symptoms.

3.5. Comparison between patients and controls on functioning scales

Patients and controls differed significantly in the multiple comparison of the different functioning variables (premorbid adjustment, disability, and global functioning) (MANCOVA: $F=313.2$; $df=195$; $p<0.001$; effect size=0.828) with socioeconomic status and parental years of education as covariates. Table 5 shows the scores obtained by patients and controls on the scales and the specific differences. Patients had significantly worse premorbid adjustment, global functioning, and disability

scores than controls. The Bonferroni test was used to control for multiple comparisons.

4. Discussion

To our knowledge, this is the largest early-onset first-episode psychosis sample ever studied and the one with the shortest duration of symptoms and psychopharmacological treatment. It was particularly difficult to recruit a sample of patients with a psychotic episode of such a short evolution. The sample was recruited from six different clinical settings in Spain. Eighty-three percent of the patients were inpatients at the time of baseline assessment. In fact, since three of the recruitment sites cover all adolescent psychiatric admissions in their geographical area, the sample provides a good representation of all children and adolescents admitted for a psychotic episode in the respective catchment areas, but it also presents a bias towards severity of symptoms or aggressivity, which are the main reasons for admission. To minimize variability and avoid population stratification, controls were of the same gender and similar age and geographical origin. The possibility of ruling out population stratification is especially important for genetic analyses, since different allelic frequencies have been described for different genetic polymorphisms in populations that are ethnically distant. Despite the fact that patients and controls came from the same type of schools and geographical areas, the SES was significantly lower in patients. Parental years in formal education were also lower in patients than in controls. This issue may be pathology-related, as it has been reported that psychotic patients have lower SES than comparison groups (McClellan et al., 1993) and parents of patients with childhood-onset schizophrenia have a greater risk of schizophrenia-spectrum disorders than parents of controls (Nicolson et al., 2003). Future analyses should include this variable as a covariant in order to rule out its possible confounding influence.

As in other studies, male patients outnumbered females (67.3% versus 32.7%). Indeed, the accepted approximate ratio in child and adolescent psychotic samples is 2:1 (Asarnow et al., 2004). There were no differences between the genders in age, SES, parental education, or global premorbid adjustment or disability scales. Recruitment increased with age; only one patient (0.9%) was 9 years old, whereas 46 (41.8%) were 17 years old. This finding is in agreement with previous studies, which show that psychotic disorders increase during puberty and adolescence and that onset prior to age 13 is rare (Werry et al., 1994; Thomsen, 1996). The mean PANSS score shows that the cases included were very severe, as in other early- and adult-onset psychosis studies.

As expected, one of the conclusions of the present study is that the vast majority of first psychotic episodes in children and adolescents are diagnosed as psychotic disorder NOS. The short duration of symptoms as an inclusion criterion may explain the fact that a very low percentage were diagnosed as schizophrenia at first evaluation and a high percentage as schizophreniform disorder. Although the diagnosis of schizophrenia may be made based on negative or affective symptoms of more than 6 months' duration, in the present sample, symptoms of longer duration were not clinically relevant enough to confirm the diagnosis of schizophrenia in the vast majority of cases. Moreover, a high percentage of mood affective disorders, both bipolar maniac and depressive type, were diagnosed. The non-specificity of diagnosis at the onset of psychotic symptoms in very young patients has been noted by other authors who also find a high percentage of psychosis NOS and mood disorders among first psychotic episodes in children (McKenna et al., 1994; Menezes and Milovan, 2000; McClellan et al., 2002; Correll et al., 2005). In the CAFEPS study, we are following the sample for 2 years and will then perform a fuller analysis of the stability and outcome of the diagnoses made during the initial evaluations. Prior to enrollment, most patients were not taking antipsychotics and, due to short duration of illness, in those who had previous exposure, this was during a very short period of time, which may be important for future analysis in which exposure to antipsychotics may be a confounding factor. In future reports, analyses of psychopharmacological treatment after assessment and at follow-up will be addressed.

Patients obtained worse scores in global functioning measured by the GAF, in disability measured by the DAS, and in infant and adolescent adjustment measured by the PAS, even after controlling for SES and years of parental education. Again, this result was expected, as previous studies (Volkmar, 1996; Ballageer et al., 2005) have already pointed out the negative influence of psychotic disorders on development and social functioning at these ages. Moreover, worse general functioning prior to the onset of a psychotic disorder has been described by other authors (Muratori et al., 2005). All of these findings support a neurodevelopment hypothesis in which, before the appearance of positive symptoms, there are already subtle difficulties in general functioning. There were positive correlations between degree of disability measured with the DAS and severity of symptoms evaluated with the PANSS. Positive

symptoms also correlated with worse general functioning and with age. Worse premorbid adjustment was slightly related to negative symptoms and total PANSS score. Other authors have also found a relationship between negative symptoms and premorbid adjustment (Haim et al., 2006). In forthcoming reports, we will present more detailed analyses of clinical characteristics and phenomenology of child and adolescent first psychotic episodes, comorbidity and variables associated with a later diagnosis of schizophrenia versus a mood disorder and psychopharmacological treatment.

One of the limitations of our study is the difficulty of establishing in advance a definitive sample size necessary to perform the data analysis, due to the low number of studies with similar design characteristics and also due to the multiplicity of analyses performed. Nevertheless, the recruitment of 110 patients makes our sample one of the largest reported to date. A second limitation is the difference in SES between patients and controls, but this variable seems to be disease-related and it will be statistically controlled for in further analyses. A third limitation is the type of centers in which the sample was recruited, as the majority were hospital settings with an inpatient facility and this may represent a bias toward inclusion of more severe cases, making it difficult to generalize conclusions to less severe or more insidious cases. Moreover, as only patients with a very short duration of positive symptoms were included, the baseline data from this study can be generalized only to acute cases of psychosis disorders and not to more chronic cases. An additional problem is the use of certain adult scales whose language is not adapted to children. This problem will require further consideration and, for some analyses, the younger children may need to be excluded. A limitation in the evaluation of the course of some of the variables may be the naturalistic treatment design of the study, but this method increases recruitment and also gives a global picture of the usual treatment and outcome in these patients. Another difficulty, as with other longitudinal studies, is the potentially high dropout rate during the follow-up period. To minimize this risk, clinical researchers are following the patients in a specific outpatient program and thus have direct personal contact with them and with their parents during the follow-up. In the control group, the economic incentive for completing the two-year assessment may also help to reduce dropouts.

The present study confirms previous findings about the characteristics of child and adolescent first psychotic episodes, such as overrepresentation of males, increased frequency of diagnoses with age, lower SES, worse premorbid adjustment and general functioning, and high prevalence of psychotic disorder NOS and mood disorders. Some of these aspects, which were expected based on the adult literature, support the continuity of adolescent-onset psychosis with adult psychosis. The CAFEPS provides the largest sample of children and adolescents with first psychotic episodes with a very short duration of initial symptoms and it is the first multicenter study to cover the main etiological, clinical, and outcome variables that have been linked to early-onset psychosis.

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