Silvia Yelmo-Cruz[a]
Armando L. Morera-Fumero[b,c]
Sunil Lakhwani[d]
Pedro Abreu-González[e]

Brain-Derived Neurotrophic Factor (BDNF) and First-Episode Psychosis. A longitudinal one-year prognosis study

[a] Servicio de Psiquiatría. Hospital Universitario de Canarias. La Laguna. Santa Cruz de Tenerife. España.
[b] Departamento de Medicina Interna, Dermatología y Psiquiatría. Facultad de Ciencias de la Salud. Universidad de la Laguna (ULL). La Laguna. Santa Cruz de Tenerife. España.
[c] Consultoría Psiquiátrica SC. Santa Cruz de Tenerife. España.
[d] Servicio de Hematología y Hemoterapia. Hospital Universitario de Canarias. La Laguna. Santa Cruz de Tenerife. España.
[e] Departamento de Ciencias Médicas Básicas: Unidad de Fisiología. Facultad de Ciencias de la Salud. Universidad de la Laguna (ULL). La Laguna. Santa Cruz de Tenerife. España.

ABSTRACT

Introduction. The brain-derived neurotrophic factor (BDNF) is a neurotrophin that has been linked to the schizophrenia neurodevelopmental hypothesis. Several studies confirm that the BDNF levels in first-episode psychosis (FEP) are lower than in healthy controls (HC). However, data about evolution of BDNF levels after a FEP and about the prognostic value of these levels are controversial.

Method. Serum BDNF levels at admission of 28 inpatients with FEP were compared with 28 HC. BDNF was also measured at discharge, three, six, nine and twelve months. BDNF levels are presented in ng/ml. We looked for correlation of BDNF levels with the psychotic symptomatology measured with the Positive and Negative Syndrome Scale (PANSS) and also the prognostic value of basal levels was evaluated to predict poor functionality (measured by the Global Assessment of Functioning) and/or relapse, as well as the subsequent diagnosis of a chronic psychotic disorder.

Results. At admission, patients BDNF levels were significantly lower than HC levels (18.52±4.51 vs. 26.55±3.22, p<0.001). At discharge FEP levels increase until HC levels (25.95±3.96 vs. 26.55±3.22, p=0,539). Upon the following determinations, BDNF FEP levels decreased, reaching the admission values, and being significantly lower than the HC and the levels at discharge (patients: three months: 19.68±3.88; six months: 19.02±4.13; nine months: 17.64±5.24; twelve months: 17.51±3.45 vs. HC: 26.55±3.22, all p<0.001). A negative correlation was found between admission BDNF levels and the PANSS negative symptoms subscale score with a trend towards significance (r=-0.303, p=0.093). BDNF levels at admission of patients with por functionality and/or relapse at 12 months were lower than BDNF levels of patients with goof functionality and without relapse, this difference had a trend towards significance. (15.38±4,72 vs. 19.57±4.06; p=0.071). We didn´t found differences between basal BDNF levels of patients who developed a chronic psychotic disorder and patients who didn't.

Conclusions. Our results reinforce the neurotrophin hypothesis. Basal levels (at diagnosis) of a FEP could predict the prognosis in terms of functionality and risk of relapse in the first year.

Key words. BDNF, first episode psychosis, schizophrenia, prognosis

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FACTOR NEUROTRÓFICO DERIVADO DEL CEREBRO Y PRIMEROS EPISODIOS PSICÓTICOS. ESTUDIO PRONÓSTICO DE UN AÑO

RESUMEN

Introducción. El factor neurotrófico derivado del cerebro (BDNF) es una neurotrofina que se ha relacionado con la hipótesis del neurodesarrollo de la esquizofrenia. Varios estudios confirman que los niveles de BDNF en el primer episodio psicótico (PEP) son más bajos que en los controles sanos. Sin embargo, los datos al respecto de la evolución de los niveles tras un PEP y el valor pronóstico de dichos niveles son controvertidos.

Método. Se compararon los niveles séricos de BDNF al ingreso de 28 pacientes hospitalizados con PEP con 28 controles sanos. También se midió el BDNF al momento

* Autor de correspondencia:
Silvia Yelmo-Cruz
Teléfono +34 606597442
correo electrónico: silviayelmo@gmail.com

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del alta, a los tres, seis, nueve y doce meses. Los niveles de BDNF se presentan en ng/ml. Se buscó correlación con la sintomatología psicótica medida con la Escala de Síndrome Positivo y Negativo (PANSS) y se evaluó en valor pronóstico de los niveles basales para predecir mala funcionalidad (medida por la Evaluación Global del Funcionamiento) y/o recaída, así como el diagnóstico ulterior de un trastorno psicótico crónico.

Resultados. Al ingreso, los niveles de BDNF de los pacientes fueron significativamente más bajos que los niveles de los controles sanos (18,52±4,51 vs. 26,55±3,22, p<0,001). Al alta los niveles de PEP aumentaron hasta niveles de los controles sanos (25,95±3,96 vs. 26,55±3,22, p=0,539). En las siguientes determinaciones, los niveles de BDNF en PEP disminuyeron, alcanzando los valores de ingreso y siendo significativamente más bajos que los controles sanos y los niveles al alta (pacientes: tres meses: 19,68±3,88; seis meses: 19,02±4,13; nueve meses: 17,64±5,24; doce meses:17,51±3,45 vs. controles sanos: 26,55±3,22, todos p<0,001). Se encontró una correlación negativa entre el BDNF al ingreso y las puntuaciones de la subescala de síntomas negativos de la PANSS con una tendencia hacia la significación (r=-0,303, p=0,093). Los niveles de BDNF al ingreso de los pacientes con mala funcionalidad y/o recaída a los 12 meses eran inferiores a los aquellos pacientes con buena funcionalidad a los 12 meses y sin recaídas, diferencia con tendencia a la significación (15,38±4,72 vs. 19,57±4,06; p=0,071). No encontramos diferencias en los niveles basales de BDNF entre los pacientes que posteriormente desarrollaron un trastorno psicótico crónico frente a los que no.

Conclusiones. Nuestros resultados refuerzan la hipótesis de las neurotrofinas. Los niveles basales (al diagnóstico) de un PEP podrían predecir el pronóstico en cuanto a funcionalidad y riesgo de recaída en el primer año.

Palabras clave. BDNF, primer episodio psicótico, esquizofrenia, pronóstico

INTRODUCTION

The first episodes of psychosis (FEP) are the form of presentation of different psychiatric disorders, among which schizophrenia stands out mainly[1]. The incidence of FEP is estimated to be 23.2 per 100,000 person-years for non-affective psychosis and 15.2 per 100,000 person-years for a first episode that progressively meets the criteria for schizophrenia[2]. The evolution and prognosis of a FEP is variable. Many patients will have a symptomatic remission, although the rate of symptomatic remissions varies in the different series and depending on the definition of remission, as well as the nature of the psychotic episode (whether it corresponds to schizophrenia or not) and can fluctuate between 15% and 70% of patients[3,4]. However, relapse of the psychosis will occur in most patients, especially if the treatment is stopped abruptly, the consumption of drugs continues, or there is a poor premorbid adjustment[5]. The relapse rate after FEP differs according to the studies, classically it has been estimated that up to 80% of patients will have a relapse in the following 5 years[6], although a more recent Spanish study observed a 3-year relapse rate of only 49.6%, being associated with a greater risk of developing a chronic psychotic disorder and an evolution with poor functionality[1].

Despite achieving symptomatic remission, most patients will not have a functional recovery, especially if the FEP represents the onset of schizophrenia[7]. Functional recovery is defined as a Global Assessment of Functioning (GAF) score > 60 and no need for hospitalization or residence in a protected apartment in the last two years[8]. Full functional recovery rates from a FEP range from 10 to 25%[9]. Some factors are associated with good functional recovery such as high premorbid functioning, lower levels of psychopathology at onset, short duration of untreated psychosis (DUP), good cognitive status, absence of symptoms depressive at the beginning, high level of education, fast response to treatment, absence of substance use at the beginning and good adherence to treatment[10]. However, to the best of our knowledge, there is no good scale or biomarker that can predict the prognosis of a FEP.

In the last 15 years, schizophrenia has been linked to the neurotrophin hypothesis. Neurotrophins are divided into Brain Derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF), Neurotrophin-3 (NT-3), and Neurotrophin-4/5 (NT 4/5)[11]. BDNF is the most abundant neurotrophin in the brain, predominantly in the hippocampus, and acts through activation of receptor tyrosine kinase B, or TrkB[12]. BDNF plays an important role in the development, proliferation, survival, regeneration, and maintenance of neuronal function in the central nervous system[13,14]. It is also involved in plasticity mechanisms, such as potentiation and long-term learning[15]. Some functions begin during prenatal development and continue through postnatal development[16,17]. It also interacts with other neurotransmitter systems that are implicated in schizophrenia, such as dopamine, glutamate, serotonin, and GABA[15]. Abnormalities in neurodevelopment or neurotransmission signaling have been found in schizophrenia, so BDNF may play a role in the pathophysiology of this disease. Other diseases have been linked to BDNF, especially neurodegenerative disorders such as Alzheimer's disease[18] and affective disorders such as depression[19] or bipolar disorder[20].

BDNF is known to cross the blood-brain barrier[21]. There is a positive correlation between serum BDNF and BDNF

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in the cerebral cortex of rodents[16], and there is a good correlation between BDNF in the prefrontal cortex and cerebrospinal fluid (CSF) samples from postmortem subjects with schizophrenia[22], as well as between the CSF and plasma BDNF in FEP or healthy controls[23]. Therefore, it is accepted that serum or plasma BDNF may reflect BDNF levels in the cerebral cortex. BDNF levels in plasma are 10 times higher than in CSF and 500 times higher in serum than in CSF[24]. This difference is because platelets act as a blood reservoir for BDNF and, when are activated to form a clot, BDNF is released.

There are numerous studies that have investigated BDNF levels in schizophrenia (in brain tissue of postmortem subjects and in serum or plasma of patients) and in FEP. In chronic schizophrenia, it appears that the BDNF concentration in the prefrontal cortex of postmortem subjects, as well as the serum and plasma levels in patients, are below controls in most studies[25-32] and several meta-analyses conclude that the BDNF blood levels are reduced in patients with schizophrenia[33-35]. Most studies conducted on FEP in serum or plasma show decreased levels of BDNF[23,36-45] and only a few do not show significant differences between FEP without prior treatment and controls[46,47]. Several meta-analyses[33,48] also conclude that basal blood levels of BDNF are reduced in patients with FEP. Attempts have been made to relate positive or negative psychotic symptomatology to BDNF levels, almost always through the Positive and Negative Syndrome Scale (PANSS), both in patients with chronic schizophrenia and in FEP, although the results are not conclusive with many discrepancies[23,36-38,40,41,44,45,49]. The evolution of BDNF levels in patients with FEP after treatment has been evaluated in several studies, also with inconclusive results[33,39,41,44,49]. There are few studies that evaluate basal BDNF levels as a prognostic factor, both as a predictor of relapse [49,50] and with functional recovery, without conclusive results [41,51].

For this reason, we have carried out a longitudinal study where we determined the basal levels of BDNF in patients with a FEP, as well as the levels every 3 months during the first year and their relationship with positive and negative psychotic symptoms and the functionality or relapse of these patients. We also investigated whether baseline BDNF levels in a FEP may be a prognostic indicator of long-term chronic psychotic disorder.

MATERIAL AND METHODS

Description

Twenty-eight (18 men/10 women) hospitalized patients with non-affective FEP without having received previous treatment participated in the study, with a mean age of 29.68±11.70 years. They were admitted to the Psychiatry Unit of the University Hospital of the Canary Islands since July 2010 until July 2011. All patients were independently diagnosed by two clinical psychiatrists (SYC and ALMF) following the Structured Clinical Interview for DSM-IV Disorders or SCID-I)[52]. We performed analytical determinations and psychopathological tests on admission, discharge, 3, 6, 9, and 12 months after discharge. Only 20 patients completed the one-year follow-up study (28 patients were included at admission and discharge, 23 patients at 3, 6, and 9 months, and 20 patients at 12-month evaluation). All patients gave their written informed consent to participate after explaining what the study consisted of, and permission was obtained from the Ethics and Research Committee of our hospital.

The exclusion criteria were suspicion of a mood disorder or affective psychosis, mental retardation prior to the onset of the disorder, pregnancy, serious illness, previous psychiatric illness, or inability to understand or sign the written consent of the patient or legal representative. Given the high prevalence of drug use in these patients, it has not been considered an exclusion factor but rather a variable to be controlled in the study design.

A complete history, physical and psychopathological examination, whole blood analysis, head CT scan, psychometric tests and BDNF levels were performed. The patients were evaluated with the PANSS[53] and the GAF[54].

The group of healthy subjects consisted of 28 people: 18 men (M) and 10 women (F) with a mean age of 31.21±11.49 years who were workers or students at the University of La Laguna and the University Hospital of the Canary Islands and had voluntarily performed a blood test. Healthy controls did not meet diagnostic criteria for any Axis I disorders (after SCID-I)[52]. We have excluded those who had mental illness, organic disease, or pregnancy.

Patients were matched with the healthy group in terms of age (patients: 29.68±11.70 vs. controls: 31.21±11.49, p=0.622), sex (patient M/F: 18/10 vs. controls M/F: 17/11, p=0.108) and body mass index (BMI) (patients: 22.61±3.13 vs. controls: 22.58±3.75, p=0.977). We analyzed other variables such as marital, educational and employment status (see Table 1).

Although the functioning criteria at a normal level or "good functioning" varies according to different authors, a GAF score equal to or greater than 61[55] is mostly accepted. We defined longitudinally two prognostic groups based on the GAF and relapses, establishing a "good prognosis group"

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(without relapse and GAF 61-100), and a "poor prognosis group" (with relapses and/or GAF 1-60) at six months and 12 months of the FEP. We also evaluated the development or not of a chronic psychotic disorder as an evolution of the FEP, reviewing the medical records of the patients ten years after developing it.

Table 1 Clinical and demographic characteristics in patients and controls

	FEP patients	Controls	P
n	*Ingreso / alta / 3 / 6 / 9 / 12m* 28 / 28 / 23 / 23 / 23 / 20	28	
Age (years)	29.68 ± 11.70	31.21 ± 11.49	0.622
Gender(female/male)	10 / 18	11 / 17	0.108
Body mass index (kg/m2)	22.61 ± 3.13	22.58 ± 3.75	0.977
Marital status (married/single)	3/25	---	---
Education (Primary/Secondary school /University)	15 / 11 / 2	---	---
Profession (employed/unemployed)	8 / 20	---	---
Tobacco smoker (yes/no)	17 / 11	2 / 26	---
Age of onset of psychosis	29 ± 11	---	---
Duration of untreated psychosis (months)	3 ± 5	---	---
Days of hospitalization	16.62±7.93	---	---
Chlorpromazine equivalent dose (mg/day)	*Admission 0* *Discharge 360.49 ± 236.12* *3 months 301.43 ± 213.06* *6 months 300.70 ± 425.68* *9 months 191.42 ± 165.19* *12 months 234.12 ± 240.46*	---	---
BDNF (ng/ml)	*Admission 18.52 ± 4.51* *Discharge 25,95 ± 3.96* *3 months 19.68 ± 3.88* *6 months 19.02 ± 4.13* *9 months 17.64 ± 5.24* *12 months 17.51 ± 3.45*	26.55 ± 3.22	---
PANSS (positive-P, negative-N, general psychopathology-GP)	*Admission P 22.78 ± 6.26* *N 17.85 ± 7.35* *GP 39.67 ± 11.24* *Discharge P 8.51 ± 1.34* *N 11.07 ± 5.26* *GP 20.11 ± 4.49* *3 months P 7.82 ± 0.8* *N 11.73 ± 5.16* *GP 20.34 ± 4.74* *6 months P 8.04 ± 1.94* *N 10.91 ± 4.89* *GP 19.56 ± 3.73* *9 months P 7.13 ± 0.45* *N 10.56 ± 4.88* *GP 18.43 ± 2.84* *12 months P 7.80 ± 1.28* *N 10.95 ± 4.92* *GP 19.75 ± 4.41*	---	---

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BDNF measurements

The first analytical extraction was performed before starting antipsychotic treatment, and subsequent laboratory extractions were performed at discharge, 3, 6, 9, and 12 months after discharge. The patients were fasting and at rest. The extraction was carried out between 08:00 and 09:00 h. The samples (two tubes without anticoagulant) were allowed to clot for about 10 minutes at room temperature and then centrifuged at 3000 rpm to separate the serum from the blood formed elements. Subsequently, the serum was divided into aliquots in Eppendorf tubes and frozen at -70°C until analysis.

Serum BDNF levels were determined using human BDNF ELISA (Enzyme-Linked ImmunoSorbent Assay) kits (Boster Biological Technology CA, USA). The manufacturer's instructions were applied both for the calibration and for the measurements of the samples. The intensity of the yellow chromogen was measured at 450 nm (λmax) in a microplate spectrophotometer (Benchmark Plus, Bio-RAD, Hercules, CA, USA). The detection limit was set at 15.5 pg/ml. The ELISA coefficients of variation (CV) were 7.2% intra-assay and 8.9% inter-assay. The calibration curve was set in a range between 31.2 and 2,000 pg/ml. The antigen-antibody reactions were carried out at a temperature of 37°C and the results of the serum BDNF levels were expressed in ng/ml.

To minimize assay variation, all serum samples were tested on the same day with the same laboratory batch and by the same analyst. Regarding the samples, the analyst was always unaware to which group they belonged or at what point in the evaluation they were.

Statistical analysis

Statistical analysis was carried out using SPSS version 19 (Statistical Package for the Social Sciences, Chicago, Illinois, USA). The comparison of qualitative variables was performed using the Chi square. It was verified if the quantitative variables complied with a normal distribution using the Shapiro-Wilk test. The comparison of quantitative variables with normal distribution was performed using the student's t test for independent or paired data. The comparison of quantitative variables that did not meet the normality condition was performed using the Mann-Whitney test for independent data or the Wilcoxon test for paired data. To evaluate the relationship between two quantitative variables, the Pearson correlation test was used when the variables had a normal distribution or the Spearman test when they did not. A significance level of ≤0.05 was accepted, while we talk about a trend towards significance with p values between 0.051 and 0.1.

RESULTS

Serum BDNF of patients with FEP at admission (18.52±4.51 ng/ml) was significantly reduced compared with healthy controls (26.55±3.22 ng/ml) (p<0.001). This difference disappeared at discharge, i.e., BDNF levels had increased ("normalized") and were like controls (discharge patients: 25.95±3.96 ng/ml versus (vs.) controls: 26.55±3.22 ng/ml, p=0.539).

If we compare by gender, that is, female patients at admission vs. discharge versus female control, there were statistically significant differences between female at admission vs. female at discharge (16.25±4.01 ng/ml vs. 25.66±4.42 ng/ml; p=0.02) and between female at admission vs. female controls (16.25±4.01ng/ml vs. 24.87±3.93 ng/ml; p=0.03), with no differences between female at discharge and female controls (25.66±4.42 ng/ml vs. 24.87±3.93 ng/ml; p=0.87). Similar results were obtained in the group of men (male at admission vs. male at discharge: 19.08±3.82 ng/ml vs. 26.12±3.74 ng/ml, p=0.01; male at admission vs. male controls: 19.08±3.82 ng/ml vs. 27.62±2.16 ng/ml, p<0.001; male at discharge vs. male controls: 26.12±3.74 ng/ml vs. 27, 62±2.16 ng/ml, p=0.41).

If we compare the serum levels of BDNF in patients between admission, discharge, 3 months, 6 months, 9 months and 12 months, there was a significant effect of the influence of time on BDNF, increasing at discharge and then gradually decreasing similar to admission levels (BDNF admission: 18.52±4.51 ng/ml; BDNF discharge: 25.95±3.96 ng/ml; BDNF 3 months: 19.68±3.88 ng/ml; BDNF 6 months: 19.02±4.13 ng/ml; BDNF 9 months: 17.64±5.24 ng/ml; BDNF 12 months: 17.51±3.45 ng/ml), the differences in BDNF levels at 3, 6, 9 and 12 months compared to the levels at discharge and compared to the levels of healthy controls were statistically significant (Figure 1).

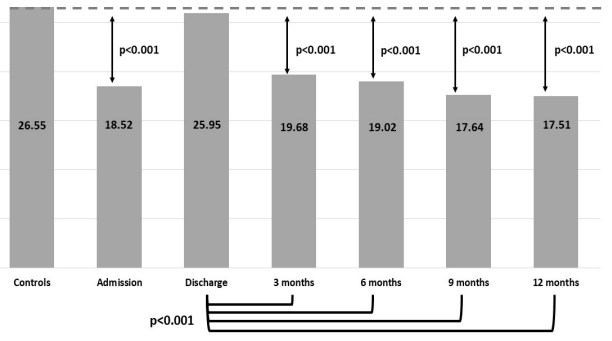

Figure 1 BDNF levels (ng/ml) in healthy controls and patients at admission, discharge and every 3 month until one year

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All the patients were drug-naïve at admission, so in the first analytical extraction there was no effect of the antipsychotic treatment. Patients received atypical antipsychotics (23 patients, 82.1%) or a combination of typical+atypical antipsychotics (5 patients, 17.9%). No patient received only typical antipsychotics. It was observed that the increase in BDNF levels throughout hospitalization (difference between discharge BDNF– admission BDNF) was greater in the group that received only atypical antipsychotics, with a trend towards statistical significance (difference in BDNF levels in the atypical antipsychotics group: 8.71±6.25 ng/ml; difference in BDNF levels in the atypical + typical group: 3.12±1.25 ng/ml; p=0.091). To analyze the effect of the doses of antipsychotics received, they were converted into chlorpromazine equivalent doses (CED)[56], with a mean at discharge of 360.5 ± 236.1 mg/day, and a mean at 12 months of 234.1 ± 240.5 mg/day. No correlation was found between the levels of BDNF and CED in any of the evaluations carried out. The results of the scores of the different PANSS subscales are shown in Table 1. Likewise, the correlation between the BDNF levels in the patients and the PANSS (PANSS-positive, negative, and general psychopathology) was analyzed. As shown in Table 2, a negative correlation was found between BDNF levels at admission and PANSS-negative (r=-0.303), with a trend towards significance (p=0.093). At discharge, this correlation disappeared and was not found at 3 months either. However, at 6 months there was a positive correlation between BDNF and PANSS-negative (r=0.366) with a trend towards significance (p=0.086), while at 9 and 12 months no significant correlation was found.

We did not find any correlation between BDNF and GAF levels in any of the six evaluations analyzed (admission, discharge, 3 months, 6 months, 9 months, and 12 months). We also analyzed whether BDNF levels at admission could predict functionality and/or relapse at 6 and 12 months. At 6 months we found that 6 patients were in the group with poor evolution (GAF between 1 and 60 and/or relapse) and 17 patients in the group with good evolution (GAF between 61 and 100 and no relapse). At 12 months we found that 5 patients were in the group with poor evolution (GAF between 1 and 60 and/or relapse) and 15 patients in the group with good evolution (GAF between 61 and 100 and no relapse). As shown in Table 3, the patients with the worst evolution have lower BDNF values at admission than those with the best evolution. At 6 months there were no significant differences, but at 12 months there is a trend towards significance (poor evolution: BDNF 15.38±4.72 ng/ml; good evolution: BDNF 19.57±4.06 ng/ml; p=0.071).

When reviewing the medical history of the 28 patients ten years later, we found that in 21 cases there was a diagnosed chronic psychotic disorder (10 patients were diagnosed with schizophrenia, 3 with schizoaffective disorder, 4 with delusional disorder, one with bipolar disorder, and in 3 cases there is an unspecified psychotic disorder). In the remaining 7 cases, the psychotic symptoms did not recur and in most the FEP corresponded to a psychosis induced by drugs. We did not find significant differences in the basal levels of BDNF on admission to the FEP between the patients who later developed a chronic psychotic disorder versus those who did not (18.53±4.55 ng/ml vs. 16.67±1.68 ng/ml; p=0.30). We also did not find significant differences in the basal levels of BDNF upon admission of the FEP between the patients who later developed schizophrenia versus those who did not (19.81±4.41 ng/ml vs. 17.25±3.72 ng/ml; p=0.13).

DISCUSSION

In this study we found that basal BDNF levels, prior to the start of antipsychotic treatment, in patients with FEP are significantly lower than in healthy controls. These results confirm what was obtained in most previous studies and several meta-analyses[23,33,36-45,48], even though some studies have not found these differences[46,47]. Longitudinally, we

Table 2 BDNF and PANSS

	BDNF admission (N=28) Correl. / signif.	BDNF discharge (N=28) Correl. / signif.	BDNF 3 months (N=23) Correl. /signif.	BDNF 6 months (N=23) Correl. / signif.	BDNF 9 months (N=23) Correl. / signif.	BDNF 12 months (N=20) Correl. / signif.
PANSS-P	0.092 / 0.643	0.080 / 0.692	0.144 / 0.511	-0.096 / 0.662	-0.173 / 0.430	0.078 / 0.745
PANSS-N	-0.303 / 0.093	-0.056 / 0.781	0.035 / 0.875	0.366 / 0.086	0.243 / 0.265	0.099/ 0.677
PANSS-PG	-0.090 / 0.649	-0.293 / 0.138	0.329 / 0.125	0.117/ 0.596	0.121 / 0.582	-0.085 / 0.720

Correl.= Pearson or Spearman correlation coefficient as appropiate; signif = significance (two-sided); PANSS-P = PANSS-positive; PANSS-N = PANSS-negative; PANSS-GP = PANSS- general psychopathology

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Table 3 BDNF and GAF

	Group	N	BDNF at admission ± sd	p
6 months	GAF 1-60 and/or relapse	6	16.55±4.88	0,260
	GAF 61-100 and no relapse	17	18.94±4.18	
12 months	GAF 1-60 and/or relapse	5	15.38±4.72	0,071
	GAF 61-100 and no relapse	15	19.57±4.06	

GAF: Global Assessment of Functioning; sd=standard deviation

found that BDNF levels in patients with FEP rise during admission after the start of antipsychotic treatment until they are practically equal to those of control subjects. Similar results have been reported by other authors[39,41,44], but some studies also do not find significant differences between baseline levels and after starting antipsychotic treatment in patients without prior treatment, although these series are small[57,58]. After this increase at discharge, later in our series, despite antipsychotic treatment, the levels decreased again and remained low throughout the entire year of follow-up, with significant differences compared to healthy controls and levels at discharge. This evolutionary pattern would explain why BDNF levels are lower in chronic schizophrenic patients than in healthy controls[33-35], and even lower than in patients with FEP[35]. It also explains that in some longitudinal studies of patients with FEP who begin follow-up after symptomatic remission, no differences in evolution have been found[49,59]. However, some authors find that after the initial elevation of BDNF levels, these levels remain elevated for 6 or 12 months[39,41]. In these studies, the patients were treated with fixed doses of an atypical antipsychotic, unlike our study, in which the patients received the treatment and dose adjustments were considered by their psychiatrist. For all these reasons, the role that antipsychotics play on BDNF levels is highly controversial, and there are even two meta-analyses with contradictory results regarding whether or not antipsychotic treatment corrects BDNF levels[33,35]. It has also been raised whether there are differences between typical or atypical antipsychotics or even between different atypical antipsychotics with an apparent greater capacity to correct BDNF levels for the atypical ones and within them clozapine or aripiprazole[30,44]. In our series, we saw how those patients who received typical + atypical antipsychotics had a greater increase in BDNF levels than those who received only atypical antipsychotics, a difference that trends towards statistical significance.

Numerous studies have sought a correlation of BDNF levels with psychotic symptoms, almost always through the PANSS scale, both in FEP and in chronic schizophrenic patients. The results of the different studies are not consistent since while some find a negative correlation between positive and/or negative psychotic symptoms[23,36-38,49,57] others find no correlation [44,45,51] or even find a positive correlation[40]. It seems logical to think that, following the neurotrophin hypothesis in schizophrenia, the correlation should be negative with lower BDNF levels in patients with more symptoms. We found a negative correlation only with negative symptoms on admission, with a tendency towards significance that was not maintained during the evolution.

Several works have attempted to relate BDNF levels to patient prognosis in different ways. On the one hand, some studies try to see if basal BDNF levels can predict relapse of the psychotic episode, without finding an association[49,50]. On the other hand, other studies have attempted to find an association with functional recovery. Thus, in one study a correlation was found between BDNF levels and the GAF score over a year[41] while in another study it was found that basal BDNF levels were lower in patients with a worse functional situation at 6 months[51]. A correlation has also been found between evolutionary levels of BDNF and cognitive functions[39]. The expression of the BDNF receptor, TrkB, which has an active full-length form and an inactive truncated form, has been identified to change during FEP of non-affective psychoses. The ratio between the expression of the active form and the basal truncated form has been shown to be predictive of the functional situation at one year[59]. We found that basal BDNF levels were lower in patients who had worse functional status at one year or who had relapsed during that year, although this difference only trended toward statistical significance. On the other hand, we found no differences between the basal BDNF levels of patients who were subsequently diagnosed with a chronic psychotic disorder versus those who were not, nor between those who were diagnosed with schizophrenia versus the rest.

There are several limitations in our study. First, the sample of patients is small, being a single center and a limited period. In addition, we had to exclude some patients because they had received some dose of antipsychotics prior to the extraction of the levels. Second, the follow-up of these patients was difficult because many dropped out. Third, the effect of individual antipsychotics was not analyzed because the number of patients treated with a single antipsychotic is small, so all antipsychotic doses were converted to CED.

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On the other hand, our study has some strengths that are worth noting. First, our patients were strictly naïve to antipsychotics at the time of inclusion. Secondly, the antipsychotic doses were modified according to the psychopathological evolution throughout the different assessments, resembling a totally real clinical situation.

CONCLUSIONS

The neurobiological hypothesis of neurotrophins has become more relevant in the last 15-20 years. From all the studies carried out to date, it can be said that BDNF plays a relevant role in the pathophysiology of FEP and schizophrenia. Its determination in serum or plasma has been assumed as a peripheral marker of what occurs in the CNS. Our results strongly support the neurotrophin hypothesis, and in this sense, basal BDNF levels could predict the prognosis of FEP. However, the current scientific evidence is not sufficient to consider it a diagnostic or prognostic biomarker of schizophrenia. More studies are needed to confirm whether it is related to psychotic symptoms, response to treatment, prognosis, and functionality. In this sense, further research on the role of BDNF in FEP is justified.

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