RAP

Review article

The impact of depot and long acting injectable antipsychotics on serum levels of brain-derived neurotrophic factor in schizophrenic and schizoaffective patients: results of a 24-month longitudinal prospective study

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Abstract

***Introduction*: Schizophrenia (SCZ) and schizoaffective disorder (SAD) are severe and complex psychiatric disorders whose liability threshold is likely modulated by the interplay of biological, mainly genetic, and environmental factors. Consistent evidence has pointed to the role of serum brain-derived neurotrophic factor (BDNF) as a plausible illness biomarker in SCZ-spectrum disorders. There is no consensus, however, on the temporal trajectory of this decline. The decrease of peripheral BDNF could be constant, with premorbid levels roughly similar to those detected in unaffected individuals, linearly declining during the course of the illness. Alternatively, BDNF peripheral levels might fluctuate in association with acute psychopathological phases of the disorder. In this context, we sought to investigate the longitudinal variation of serum BDNF levels over 24 months in a cohort of Sardinian patients [Longitudinal Assessment of BDNF in Sardinian Psychotic patients (LABSP)]. Here, we present a secondary analysis of LABSP data, focusing on the impact of antipsychotic therapy, particularly depot and long-acting injectable (LAI), on the longitudinal trajectory of serum BDNF levels. Further, we tested whether genetic variation within the gene encoding for BDNF could moderate the relationship between BDNF serum levels and drug treatment.**

***Methods*: LABSP patients were assessed every six months for a series of psychopathological, cognitive and drug-related measures, as well as for BDNF serum levels over 24-month. Blood samples for each patient were taken at the same time of the day (between 8:00 and 10:00 AM). BDNF serum levels were determined using BDNF ELISA Kit. Four tag single nucleotide polymorphisms (SNPs) within BDNF gene (rs1519480, rs11030104, rs6265 (Val66Met), and rs7934165) were selected using standard parameters and analyzed with Polymerase Chain Reaction (PCR). Mixed-effects linear regression models (MLRM) was used to analyze longitudinal data.**

***Results*: Twenty-four patients out of 105 LABSP (22.9%) patients received therapy with depot/LAI. Analysis with MLRM showed a significant effect of depot/LAI treatment associated with increasing serum BDNF levels ($Z = 1.9$, $p = 0.053$). However, oral antipsychotics did not significantly impacted on the longitudinal trajectory of serum BDNF levels ($Z = 0.15$, $p = 0.9$). There was no moderating effect of variants within BDNF gene on the identified association.**

***Conclusions*: Our study identified a significant longitudinal increase of serum BDNF in SCZ and SAD patients treated with depot/LAI antipsychotic therapy. The identification of a significant impact of this preparation of antipsychotic treatment on serum BDNF despite the limited sample size,**

points to a moderate to large magnitude of effect that should be investigated in future prospective studies.

KEY WORDS: antipsychotics, LAI, depot, complex disorders, longitudinal studies, biomarker.

Introduction

Schizophrenia (SCZ) is a severe, chronic mental disorder characterized by the presence of core psychopathological symptoms such as delusions and hallucinations (positive symptoms), impaired motivation and social withdrawal (negative symptoms), and cognitive impairment (1). As a complex disorder, the liability threshold for SCZ is likely modulated by the interplay of biological, mainly genetic, and environmental factors (2, 3). Indeed, family, twin and adoption studies have demonstrated the presence of a substantial genetic contribution to the risk of SCZ (4). This has prompted molecular genetics studies, particularly genome-wide analyses, which have identified hundreds of genes significantly associated with the risk of SCZ (5). Similarly, schizoaffective disorder (SAD) has substantial heritability (6), and molecular studies suggest a specific influence of genetic determinants on its risk (7). In addition, as observed in SCZ, environmental factors appear to modulate the liability threshold for SAD determined by its genetic architecture (8).

In this context, researchers have attempted to take advantage of the increased knowledge on the genetic and biological make-up of these complex disorders to develop predictive risk models. One approach takes advantage of findings from genome-wide association studies (GWAS) and estimates the genetic correlation between pairs of complex traits using polygenic risk scoring (PRS) (9). For instance, SCZ PRS associated significantly with decreased cognitive function in a large sample of older adults (10).

Another strategy consists of testing whether risk prediction in complex psychiatric disorders can rely on biomarkers, either based on neuroimaging or detectable in peripheral tissues such as serum, plasma or cerebrospinal fluid (CSF). Concerning the latter group, consistent evidence has pointed to the role of serum brain-derived neurotrophic factor (BDNF) as a plausible illness biomarker in SCZ-spectrum disorders (11, 12).

Indeed, there is consistent evidence that chronic and medicated SCZ patients (13-18), as well as first episode and medication naïve (19-23), present a significant decrease in serum BDNF levels compared to healthy individuals. However, the presence of discordant findings showing increased or unchanged BDNF serum levels in SCZ patients compared to healthy controls (24-27) prompted researchers to perform quantitative meta-analytical estimates. Indeed, Fernandes et al. (12) showed that SCZ is associated with a moderate decrease of serum and plasma BDNF levels compared to healthy controls.

There is no consensus, however, on the temporal trajectory of this decline. The decrease of peripheral BDNF could be constant, with pre-morbid levels roughly similar to those detected in unaffected individuals, linearly declining during the course of the illness. Alternatively, BDNF peripheral levels might fluctuate in association with acute psychopathological phases of the disorder. Indeed, meta-analytical estimates have shown that BDNF decreases significantly in relation to illness activity (11). In addition, a critical factor modulating peripheral BDNF levels in SCZ-spectrum disorders is drug therapy. Quantitative data synthesis shows small but significant increases of serum BDNF levels under antipsychotic treatment (12), although existing studies have length of follow-up not longer than one year.

Another factor that might modulate variation in peripheral levels of BDNF in SCZ-spectrum subjects is genetics. Indeed, the Val66Met polymorphism of BDNF gene impacts activity-dependent secretion of BDNF (28). Thus, some studies have found that this functional variant can influence serum BDNF levels (29-31). Specifically, carriers of Met allele showed lower serum BDNF levels compared to those carrying Val allele (29, 30), although one study found the contrary (31).

In this context, we sought to investigate the longitudinal variation of serum BDNF levels over 24 months in a cohort of Sardinian patients [Longitudinal Assessment of BDNF in Sardinian Psychotic patients (LABSP)] (32). LABSP patients were assessed every six months for a series of psychopathological, cognitive and drug-related measures, as well as for BDNF serum levels (32). Here, we present a secondary analysis of LABSP data, focusing on the impact of antipsychotic therapy, particularly depot and long-acting injectable (LAI), on the longitudinal trajectory of serum BDNF levels. Further, we tested whether genetic variation within the gene encoding for BDNF could moderate the relationship between BDNF serum levels and drug treatment.

Subject and methods

Sample

The sample of SCZ and SAD patients was recruited at the community mental health centre of the Psychiatry Research Unit of the Department of Medical Science and Public Health, University of Cagliari and University of Cagliari Health Agency, Cagliari, Italy. The diagnosis of SCZ or SAD was confirmed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (SCID-I/P) (33) administered by trained mental-health professionals (psychiatry residents and/or senior clinical staff). Patients were recruited in LABSP if they fulfilled the following inclusion criteria: 1) age between 18 and 65 years; 2) diagnosis of SCZ or SAD according to DSM-IV-TR; and 3) stability during the six months before recruit-

ment. Exclusion criteria were: 1) refusal to provide consent; 2) presence of acute psychopathological symptoms; 3) presence of illness-related cognitive impairment of such severity that affects their ability to cooperate; 4) presence of major unstable medical illness; 5) severe mental retardation; 6) major neurological disorder or previous head injury; 7) current drug and alcohol dependence. Given the characteristics of the patient population followed-up at our community mental health centre, our sample was not comprised of drug-naïve patients and was on a pharmacological treatment regime mainly based on antipsychotics.

Assessment procedures

Details of the assessment procedures have been previously published (32). Briefly, blood samples from recruited patients were taken at baseline (T_0), and at four consecutive time points: 6 months (T_1), 12 months (T_2), 18 months (T_3), and 24 months (T_4). Detailed information on ongoing pharmacological treatment regime was collected through direct assessment of the proband and an accurate review of available medical records.

Sampling and assessment of BDNF serum levels

Blood samples for each patient were taken at the same time of the day (between 8:00 and 10:00 AM). BDNF serum levels were determined using BDNF ELISA Kit (Booster Immunoleader, Cat. N° EK0307) for the quantitative detection of human BDNF in cell culture supernatants, serum and plasma. This kit is based on a standard sandwich enzyme-linked immune-sorbent assay technology for specific quantifications of natural and recombinant human BDNF with a high sensitivity (< 2 pg/mL) and with no detectable cross-reactivity with other relevant proteins. After blood sampling, serum was allowed to clot in a serum separator tube for about 4 hours at room temperature. After that it was centrifuged at approximately 1000 X g for 15 min. Supernatant serum samples was collected in small aliquot and stored immediately at -20°C for future analysis. Then, samples were processed according to kit protocol and instructions. Optical density absorbance of each sample was read with a 450nm filter in a microplate reader (Thermo Scientific Multiskan FC) within 30 minutes after the final step of the kit procedure. Data obtained was analysed using the Thermo Scientific SkanIt Software 3.0 for Multiskan FC.

Genetic analysis

Tag single nucleotide polymorphisms (SNPs) were selected using Tagger tool in Haploview (v4.2) based on linkage disequilibrium (LD), by including SNPs with $r^2 \geq 0.8$, and with a minor allele frequency threshold of 0.01. Genotyping of the following BDNF SNPs rs1519480, rs11030104, rs6265 (Val66Met), and rs7934165 was carried out using TaqMan probe on demand (C_11592757_20, C_1751792_10, C_11592758_10, C_1197567_10, Thermofisher) on a StepOne Plus instrument (Thermofisher). Primers were marked in VIC and FAM to discriminate between alleles. The reaction was carried out in 10 ul final volume, containing 5 ul of MasterMix (2X), 0.5 ul of probe assay (20X), 1ul of cDNA and 3.5 ul of RNA-free water. Polymerase Chain Reaction (PCR) settings were the following: 30 sec. 60°C, 10 min 90°C, and 40 cycles at 95°C for 15 sec and 60°C for 1 min.

Data analysis

Mixed-effects linear regression models (MLRM) was used to analyze longitudinal data (34, 35). Specifically, we regressed independent variables (both categorical and continuous) on BDNF serum levels (dependent variable). We used MLRM as this approach allows to model individual change over time and appears to be more flexible in terms of repeated measures, particularly when the number of observations per subject is not the same at each time point (34, 35). Further, these models allow generalization of non-normally distributed data for independent variables. We used MLRM to analyze the impact of oral antipsychotic and/or depot LAI therapy on the longitudinal variation of BDNF levels. Specifically, these independent variables were regressed on BDNF serum levels while correcting for age and sex. Finally, each BDNF SNP was added to MLRM as covariate while correcting for age and sex to check for a possible moderating effect. All data were analyzed using "lme4" package implemented in R (36). Missing data for independent variables was dealt with the "na.action" function implemented in R. The statistical significance of identified MLRM was calculated using the "multcomp" R package. Finally, graphical representation of MLRM was obtained with R packages "sJPlot" e "sjmisc".

Results

Sample characteristics

The sample included 105 patients, 64 with a diagnosis of SCZ and 41 with SAD. The main clinical and demographic characteristics of the sample are detailed in Table 1. Relevant to this study is the number of subjects who were treated with oral antipsychotic therapy at the time of recruitment (T_0) (N = 103, 98%) and those who received therapy with depot/LAI over the course of the study (N = 24, 22.9%). Importantly, a proportion of patients treated with depot/LAI had concomitant oral antipsychotic therapy.

The impact of oral antipsychotics and depot/LAI therapy on the longitudinal trajectory of serum BDNF levels

Analysis with MLRM did not show a significant influence of treatment with oral antipsychotics on the longitudinal trajectory of serum BDNF levels (Model 1: Z = 0.15, p = 0.9) (Table 2). This was confirmed when we added sex and age as covariates (Model 2: Z = 0.003, p = 0.9). We than tested the effect of

Table 1. Main demographic and clinical characteristics of the LABSP sample.

Variable (continuous)	N	Mean	SD
Age, years	105	48.85	10.45
Education, years	105	9.26	3.23
Offspring, N	105	0.34	0.95
Age of onset, years	105	21.77	9.30
Duration of illness, months	105	308.51	134.33
Age at first treatment, years	105	24.23	8.95
Duration of untreated illness, months	105	29.07	54.60
Antipsychotics, chlorpromazine equivalents, mg/die	103	378.92	272.3
Variable (categorical)	**N**	**%**	
Sex (male)	74	70.5	
Age class			
18-20	2	1.9	
21-25	38	36.2	
26-44	58	55.2	
45-65	7	6.7	
Marital status			
Single	8	7.6	
Married/Cohabiting	10	9.5	
Divorced	2	1.9	
Widowed	83	79.0	
NA	2	1.9	
Presence of offspring	19	18.1	
Employment			
Employed	7	6.7	
Student	1	1.0	
Registered disabled civilian	95	90.5	
Unemployed	2	1.9	
Presence of smoking	52	49.5	
History of substance abuse	28	30.8	
Current use of substances	5	5.5	
Presence of family history of mental disorders	64	61.0	
Long-acting antipsychotic therapy	24	22.9	

NA: not available, SD: standard deviation.

depot/LAI therapy, identifying a marginally significant effect on serum BDNF levels over 24 months. Specifically, the subgroup of patients treated with depot/LAI had an increase in serum BDNF levels (Z = 1.9, p = 0.053). The strength of this association increased when the above covariates were included in the model (Z = 2.2, p = 0.03).

Moderating effect of BDNF genetic variation

In light of these results, we tested whether the four polymorphisms within BDNF gene might influence the impact of depot/LAI therapy on the longitudinal trajectory of serum BDNF levels. As shown in Table 3, no SNP significantly moderated the identified association. These models were tested without other covariates to avoid saturation of the MLRM.

Discussion

Our secondary analysis of LABSP data found that treatment with depot/LAI, but not with oral antipsy-

Table 2. Results of mixed-effects linear regression models.

Model	Indipendent variable	Estimated coefficient	Standard error	Z	p
Model 1	Time	-0.008	0.002	-5.0	**6.3×10^{-7}**
	Oral antipsychotic	0.00001	0.00009	0.15	0.9
Model 2	Time	-0.008	0.002	-4.9	**1.0×10^{-6}**
	Oral antipsychotic	-3×10^{-7}	0.00009	0.003	0.9
	Age	-0.002	0.003	-0.8	0.4
Model 3	Time	-0.08	0.02	-5.1	**3.9×10^{-7}**
	Depot/Long-acting	0.11	0.06	1.9	**0.053**
Model 4	Time	-0.08	0.02	-5.0	**6.7×10^{-7}**
	Depot/Long-acting	0.13	0.06	2.2	**0.03**
	Age	-0.004	0.003	-1.3	0.2

p, p-value.

Table 3. Mixed-effects linear regression models including BDNF genetic variants.

Model	Indipendent variable	Estimated coefficient	Standard error	Z	p
Model 1	Time	-0.08	0.002	-4.6	**3.5×10^{-6}**
	Depot/Long-acting	0.19	0.07	2.7	**0.006**
	rs7934165 A/G	0.05	0.07	0.7	0.5
	rs7934165 G/G	0.02	0.09	0.2	0.8
Model 2	Time	-0.08	0.002	-4.7	**2.9×10^{-6}**
	Depot/Long-acting	0.17	0.07	2.5	**0.01**
	rs6265 (Val66Met) C/T	0.03	0.07	0.5	0.6
	rs6265 (Val66Met) T/T	0.01	0.11	0.06	0.9
Model 3	Time	-0.08	0.02	-4.7	**3.1×10^{-6}**
	Depot/Long-acting	0.17	0.07	2.5	**0.02**
	rs1519480 C/T	0.09	0.3	0.3	0.7
	rs1519480 C/T	0.13	0.3	0.5	0.6
Model 4	Time	-0.08	0.02	-4.7	**3.3×10^{-6}**
	Depot/Long-acting	0.2	0.07	2.5	**0.01**
	rs11030104 A/G	0.06	0.06	0.9	0.34
	rs11030104 A/G	0.05	0.1	0.4	0.6

p, p-value.

chotics, significantly impacted on the longitudinal trajectory of serum BDNF levels over the time of follow-up. Specifically, the 24 patients treated with depot/LAI presented a longitudinal increase in serum BDNF levels. This finding is consistent with a number of preclinical (37-39) and clinical (12) studies. With regard to preclinical evidence, Park et al. (38) showed that chronic (21 days) treatment with quetiapine attenuated the hippocampal decrease of BDNF induced in rats through immobilization stress. These Authors subsequently suggested that this effect of antipsychotics on BDNF might be class-specific, with second-generation (aripiprazole and olanzapine), but not first-generation antipsychotics (haloperidol), effective in restoring the loss of BDNF induced by immobilization stress (39). This finding is partly concordant with the work of Pillai et al. (37), showing that striatal and hippocampal levels of BDNF in rats decreased after 90 days of treatment with haloperidol but were significantly restored after switching to a subsequent 90-day treatment with either olanzapine or risperidone. Indeed, other Authors have suggested that first- (haloperidol) or second-generation (risperidone) antipsychotics can reduce BDNF levels in rat brain (cortex and hippocampus) (40, 41). This discrepancy might be reconciled by taking into account antipsychotics dosage (42). Indeed, Chlan-Fourney et al. (42) observed that intermediate doses of risperidone had no effect on BDNF hippocampal levels in rats, suggesting that higher chronic doses of antipsychotics might determine long-term down-regulation of BDNF in the brain. Concerning clinical evidence, our results are consistent with the meta-analysis by Fernandes et al. (12) which analyzed 14 longitudinal

studies (total N = 463) showing that the use of antipsychotics was associated with a small but significant increase in serum and plasma BDNF levels. Of importance, this increase in BDNF serum and plasma levels was independent of treatment response [defined as at least 40% reduction in the Positive and Negative Symptoms Scale (PANSS) total score], but, differently from our work, was mainly led by studies showing a raise in plasma levels of BDNF rather than in serum (12).

Another finding of our secondary analysis is the discrepant effect of oral and depot/LAI antipsychotic therapy on serum BDNF levels. This might be explained by at least two factors: 1) the increased adherence among patients treated with depot/LAI intrinsic to the nature of this therapy, and 2) the specific pharmacokinetics of depot/LAI formulation. Concerning the first aspect, it is known that depot/LAI preparations have many advantages over oral therapy, such as not having to remember to take drugs daily, reducing the risk of unintentional or deliberate overdose, and transparency of adherence (43, 44). Secondly, depot/LAI have a more consistent bioavailability (43) and reduced peak-trough plasma levels (45) ensuring a more effective action of the drug centrally (44, 45). These factors can explain the presence of an increase in BDNF serum levels specific to the subgroup of patients receiving depot/LAI treatment in our study. Indeed, preclinical studies show that serum BDNF increases significantly in rats administered continuously (4-6 weeks which equals > 3 years in humans), but not intermittently, with risperidone (46).

A final remark concerns the absence of a moderating effect of genetic variants within the BDNF gene on the significant impact of depot/LAI therapy on the serum levels of this neurotrophin. This is consistent with the quantitative data-synthesis of 13 studies performed by Terracciano et al. (47) showing that the Val66Met genetic polymorphism was not associated with BDNF serum levels, a finding corroborated by the GWAS analysis in a large cohort of Sardinian individuals (N = 2,054). Consistent with the high pattern of LD among the SNPs investigated in this study, no BDNF genetic variant significantly moderated the identified patterns of association. However, it is possible that the genetic effects of BDNF polymorphism on its serum levels are of such small magnitude that only studies with very large sample size will be able to detect a significant effect.

Our results should be interpreted in the context of several limitations. First, the subgroup of patients treated with depot/LAI has a limited sample size, a factor that hindered further secondary analysis (for instance testing an antipsychotic class-specific effect). However, it should be noted that the identification of a significant pattern of association between depot/LAI and serum BDNF in such a small subgroup of patients points to the presence of an effect size of moderate to large magnitude that should be investigated in future prospective studies. Secondly, given the limited sample size of the subgroup treated with depot/LAI, MLRM were run with a limited number of covariates to avoid saturation of models. Nevertheless, all tested models converged flawlessly suggesting their relative stability. Finally, it is possible that changes in a serum biomarker might not be representative of modifications at the brain level. However, the identification of a peripheral marker, such as serum BDNF, associated with a specific trait or phenotype, such as treatment with depot/LAI, might not necessarily provide with mechanistic insights on the pathophysiology of the disorder under study, but might rather be of prognostic utility in clinical settings.

Conclusions

In summary, our study identified a significant longitudinal increase of serum BDNF in SCZ and SAD patients treated with depot/LAI antipsychotic therapy. The identification of a significant impact of this preparation of antipsychotic treatment on serum BDNF despite the limited sample size, points to a moderate to large magnitude of effect that should be investigated in future prospective studies.

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