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Inflammatory markers in antipsychotic-naïve patients with nonaffective psychosis and deficit vs. nondeficit features

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ABSTRACT

Newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis appear to have increases in pro-inflammatory cytokines. Patients characterized by primary, enduring negative symptoms (deficit symptoms) differ from patients without such features with regard to course of illness, treatment response, risk factors and metabolic disturbances. We hypothesized that they would also differ on concentrations of the inflammatory markers interleukin-6 (IL6) and C-reactive protein (CRP). Newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis were categorized into deficit ($N=20$) and nondeficit ($N=42$) groups, and were matched on age, gender, body mass index, smoking, cortisol level, socioeconomic status, and the severity of psychotic symptoms. Fasting concentrations of IL6 were significantly higher in deficit (mean [S.D.]) (8.0 pg/ml [12.7]) than nondeficit patients (0.3 pg/ml [1.3]). CRP levels were also significantly higher in the deficit patients (0.3 mg/dl [0.4]) vs. (0.2 mg/dl [0.4]), respectively. In contrast, 2-h glucose concentrations (2HG) in a glucose tolerance test were lower in the deficit than the nondeficit group. Our results show a double dissociation with regard to glucose intolerance and inflammation: the deficit group has greater inflammation, but less severe glucose intolerance. These results provide further evidence for the validity of the deficit/nondeficit categorization.

1. Introduction

Schizophrenia subtypes have long been the topic of research. One proposed subtype is deficit schizophrenia, which is characterized by primary (or idiopathic), enduring negative symptoms. Deficit/nondeficit differences in the course of illness, signs and symptoms other than negative symptoms, risk factors, biological correlates, and treatment response have all been found (Kirkpatrick et al., 2001). In some studies, despite the presence of primary negative symptoms, the deficit group did not have a more severe form of the same abnormality found in nondeficit schizophrenia. Instead, with regard to some variables, the deficit group was either less severely affected than the nondeficit group, or neither group was more severely affected, but both differed from control subjects (e.g., excess winter birth in nondeficit schizophrenia vs. excess summer births in deficit schizophrenia) (Messias et al., 2004).

A number of studies have found increased pro-inflammatory markers in patients with schizophrenia (Miller et al., 2011). Inflammation is governed by the interaction of multiple specific mediators including cytokines, prostaglandins, and chemokines. One of these mediators, c-reactive protein (CRP), an acute-phase protein, is a general marker of inflammation. Increased levels of CRP have been associated with increased risk of inflammatory cardiovascular disorders (Lowe, 2005). In schizophrenia patients, CRP has been associated with cognitive impairment (Dickerson et al., 2007), more severe psychopathology (Fan et al., 2007), and certain clinical phenotypes (Akanji et al., 2009). Although CRP values were found to be increased in treated schizophrenia patients (Carrizo et al., 2008), the difference was not replicated in a drug-naïve sample compared with matched control subjects (Fernandez-Egea et al., 2009).

Interleukin-6 (IL6) is a multifunctional cytokine with biological activities that include regulation of immune response, inflammation, and haematopoiesis. IL6 induces T-cell proliferation, systemic inflammatory symptoms such as fever, generalized fatigue, and anorexia

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and angiogenesis by augmenting the production of vascular endothelial growth factor. It also has both neurotrophic and neurotoxic effects in different neuronal types and at different developmental stages (Deverman and Patterson, 2009). One of these effects is stimulation of CRP production (Papanicolaou and Vgontzas, 2000). We had previously shown that glucose tolerance differs between deficit and nondeficit schizophrenia patients (Kirkpatrick et al., 2009). In the current study, we tested the hypothesis that patients with psychosis and deficit features would also differ from patients without these features (nondeficit patients) with regard to IL6 and CRP concentrations.

2. Materials and methods

2.1. Subjects

Newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis were assessed at the time of their first contact with psychiatric services. In addition to patients with schizophrenia, patients with schizophreniform disorder, delusional disorder, and psychosis not otherwise specified were included because these disorders share clinical and genetic factors with schizophrenia, and most newly diagnosed individuals with these disorders receive a diagnosis of schizophrenia within the first year after first clinical contact (Addington et al., 2005). Subjects with schizoaffective disorder were not included. The patients had a maximum cumulative lifetime exposure to antipsychotics of 1 week, and no antipsychotic use in the 30 days before study entry.

The setting was an academic medical center in Barcelona that provides health services for residents of the surrounding catchment area as part of the Spanish national health care system. The catchment area is a relatively homogeneous, middle class/upper middle class neighborhood in the center of Barcelona. Further details on this study have been presented (Fernandez-Egea et al., 2009).

Additional inclusion and exclusion criteria for all subjects were as follows: 1) age from 18 to 64 years, 2) no history of diabetes or other serious medical or neurological condition associated with glucose intolerance or insulin resistance (e.g. Cushing's disease), 3) not taking a medication associated with insulin resistance (hydrochlorothiazide, furosemide, ethacrynic acid, metolazone, chlorthalidone, beta blockers, glucocorticoids, phenytoin, nicotinic acid, cyclosporine, pentamidine, or narcotics), and 4) no history of cocaine use in the previous 30 days.

2.2. Assessments

All subjects were interviewed using the Spanish translation of the Structured Clinical Interview for DSM-IV Axis I Disorders, clinician version (SCID-I). They were also administered the Dartmouth Assessment of Lifestyle Inventory to quantify substance abuse. Socioeconomic status (SES) was assessed using the Hollingshead–Redlich scale (Hollinshead and Redlich, 1958).

2.3. Procedure

All participants were given a 2-h, 75-g oral glucose tolerance test, which began between 08.00 and 09.00 h after an overnight fast. Samples for IL6, CRP, and cortisol blood concentrations were also taken before the patients ingested glucose. They were allowed to receive anti-anxiety medication (lorazepam) the night before blood was drawn to a maximum of 3 mg, but not on the day of assessment. No correlation was found between lorazepam administration and the variables studied. Height, weight, and waist and hip circumference, when wearing underwear and without shoes, were recorded between the baseline and two blood samples. The determination of IL6 was performed with a commercial enzyme immunoassay technique (Biosurce, Nivelles, Belgium). Cortisol was measured using a radioimmunoassay (Immuchem, Ivoz-Ramet, Belgium).

2.4. Deficit/nondeficit categorization

Patients were categorized into groups with and without deficit features using the Proxy for the Deficit Syndrome, or PDS (Kirkpatrick et al., 1993, 1996a,b,c, 1998, 2000, 2002a,b, 2003, 2009; Messias and Kirkpatrick, 2001; Tek et al., 2001; Messias and Bienvenu, 2003; Messias et al., 2004; Chemerinski et al., 2006; Dickerson et al., 2006; Kirkpatrick and Galderisi, 2008; Wang et al., 2008; Arango et al., 2011). Patients' ($N=95$) deficit/nondeficit symptomatology was assessed with the Positive and Negative Syndrome Scale (PANSS) item scores; the PANSS rating was completed on the day of the glucose tolerance test, before any of the blood measures were available to the investigators. Each patient was assigned a PDS score as defined by PANSS item scores as follows: PDS = blunted affect + lack of spontaneity and flow of conversation − (hostility + guilt + anxiety + depressive mood). This score quantified the combination of prominent negative symptoms and a lack of distress that is characteristic of deficit compared with nondeficit patients (Kirkpatrick et al., 1993, 1994), with high scores reflecting deficit-like features (high negative symptom scores and an absence of dysphoria) and low scores reflecting their absence. These scores ranged from −11 to 5. Patients with high PDS scores (below −1) were assigned to the putative deficit group ($N=24$), while the other patients (PDS scores over 0) were designated nondeficit ($N=71$).

The deficit and nondeficit groups were matched, without knowledge of outcome variables, on age, gender, smoking, body mass index (BMI), and socioeconomic status (SES) of the family of origin by omitting nondeficit patients until these variables were very similar for the two groups. Due to lack of matched data on several patients, our total number decreased from 95 to 62. The validity of these two matched groups, deficit ($N=20$) and nondeficit ($N=42$), was tested by comparing the features of the two groups with those found in deficit and nondeficit groups in other studies (Kirkpatrick et al., 2001). In addition to high negative symptoms and an absence of dysphoria (present in that group by definition, because of the use of the PDS), a valid deficit group, compared with nondeficit subjects, would not have a greater length of illness or more severe psychotic symptoms. In our examination of psychotic symptoms, the sum of the delusions and hallucinatory behavior items on the PANSS was analyzed separately from the conceptual disorganization item. Physical examination and other laboratory tests did not reveal the presence of infection in these patients, and in this relatively young group, no one met criteria for the metabolic syndrome.

2.5. Statistical analysis

We conducted two sets of analyses. In the first set of analyses, deficit and nondeficit groups were matched for age, gender, body mass index, and smoking (the last variable was highly correlated with all drug abuse). This matching made it necessary to omit some nondeficit patients from the first set of analyses. Only those subjects with data on all of the relevant variables were included, yielding matched groups of 20 deficit and 42 nondeficit subjects. Matching was done without knowledge of IL6 and CRP concentrations. Because the IL6 and CRP values were not normally distributed, these variables were log-transformed for all analyses. In order to assess the robustness of our results with the matched sample, we also conducted logistic regression analysis among patients who were not matched. In bivariate correlations, age had a correlation <0.20 with both IL6 and CRP (both log-transformed), whereas gender, smoking, BMI, and SES all had a correlation >0.40. Given these results, we conducted two analyses; in each, deficit vs. nondeficit categorization was the dependent variable. In one of these analyses, log-transformed IL6 and age were the independent variables, while in the other analysis, log-transformed CRP and age were the independent variables. Because of some missing data, there were 21 deficit and 67 nondeficit subjects in the IL6 analysis versus 23 deficit and 64 nondeficit subjects in the CRP analysis.

Statistical tests were performed using version 17.0 for Windows of SPSS (Statistical Package for the Social Sciences).

3. Results

The validity of the categorization was good, as demonstrated by the clinical and demographic features of the matched deficit and nondeficit groups (see Table 1). Both groups were overwhelmingly composed of Spanish Caucasians. By definition, the deficit group had more severe negative symptoms but less dysphoria than the nondeficit group, but there was no significant difference in demographic characteristics or positive psychotic symptoms.

Both IL6 and CRP concentrations were significantly higher in the deficit than the nondeficit group (see Table 1). In contrast, 2-h glucose concentrations in the glucose tolerance test were significantly higher

Table 1
Demographic, clinical, and metabolic characteristics of patients with and without deficit features.

	Deficit ($N=20$)	Non deficit ($N=42$)	p value
Age	29.8 (9.8)	27.7 (6.5)	0.40
% Gender (male)	67	61	0.58
Cigarettes/day	4.7 (6.9)	6.8 (7.9)	0.32
Body mass index[a]	23.4 (2.5)	22.5 (4.3)	0.41
SES[b]	5.0 (2.2)	5.3 (2.3)	0.68
PANSS items scores:			
Disorganization	3.9 (1.8)	3.5 (1.4)	0.34
Reality distortion[c]	8.1 (3.3)	8.2 (2.2)	0.82
IL6 (pg/mL)[d]	8.0 (12.7)	0.3 (1.3)	<0.001
CRP (mg/dL)[d]	0.3 (0.4)	0.2 (0.4)	0.01
2HG (mg/dL)	99.1 (25.1)	119.2 (36.9)	0.03
Cortisol	18.7 (5.9)	17.4 (5.9)	0.43

Values are mean (S.D.), except for % male.
P values are from t-test, except for % male (chi-square) and cigarettes (Mann–Whitney U).
[a] $N=19$ for the deficit group.
[b] For deficit $N=14$ and nondeficit $N=37$.
[c] Reality distortion scores = scores for hallucinations + delusions.
[d] IL6 and CRP values were analyzed using log-transformed data.

in the nondeficit than the deficit group. Cortisol values were similar in the two groups. The effect size for log-transformed IL6 was 1.1, much greater than the normal definition of a large effect size; the effect size for the log-transformed CRP values was 0.86, which also represents a large effect size.

In the logistic regression analyses, consistent with the results in the smaller matched sample, the deficit group had significantly higher IL6 and CRP values (respective p values <0.001 and <0.03; data not shown). There was no relationship between the inflammatory markers and duration of untreated psychosis (data not shown).

4. Discussion

In this study, newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis and features of deficit schizophrenia were found to have higher IL6 and CRP concentrations than did matched patients without deficit features. These findings could not be attributed to confounding by age, gender, SES of the family of origin, BMI, smoking status, cortisol concentrations, positive psychotic symptoms, antipsychotic use (as the subjects were antipsychotic-naïve), or antidepressant or mood-stabilizing drugs (no subject had previous use of an antidepressant or a mood-stabilizer). In contrast, the group with deficit features had lower glucose concentrations than did those without these characteristics, as we had previously shown in a sample that overlapped substantially with the current subjects (Kirkpatrick et al., 2009).

4.1. Study limitations

A limitation of our study is that the number of subjects with deficit features was limited. However, the limited sample size should have been biased toward a negative result because of poor statistical power. Another limitation was that our putative deficit/nondeficit categorization was made using the PDS, rather than the Schedule for the Deficit Syndrome, the standard instrument used to distinguish patients with and without primary negative symptoms (Kirkpatrick et al., 1989). The categorizations in this study were validated by comparison to the clinical features of deficit and nondeficit groups diagnosed in the literature; the groups in this study were very similar in their characteristics to those diagnosed by the Schedule for the Deficit Syndrome (SDS). Moreover, the Proxy for the Deficit Syndrome has been validated in a number of previous publication (Kirkpatrick et al., 1993, 1996a, 1996b, 1996c, 1998, 2000, 2002a, 2002b, 2003, 2008, 2009; Messias and Kirkpatrick, 2001; Tek et al., 2001; Messias and Bienvenu, 2003; Messias et al., 2004; Chemerinski et al., 2006; Dickerson et al., 2006; Kirkpatrick and Galderisi, 2008; Wang et al., 2008; Arango et al., 2011). The use of the PDS also should have been biased toward a negative study because of miscategorizations compared to use of the SDS. The large effect sizes we found suggest these differences are robust, but replication is needed. We only examined IL6 and CRP as inflammatory markers; examination of others, such as tumor necrosis factor-alpha would be desirable.

4.2. Conclusions

Our results represent a double dissociation in metabolic measures, with greater inflammation but less severe glucose intolerance in the deficit group. (We have previously shown that both patient groups differ from matched control subjects.) Higher CRP concentrations in the deficit group are consistent with a previous study in which treated patients with high CRP values had higher scores on the negative symptom subscale of the PANSS (Fan et al., 2007). Our results are also consistent with other studies in which elevated concentrations of IL6 were found in patients with predominantly negative symptoms and/or poor therapy outcome (Schwarz et al., 2001), longer duration and an unfavorable course (Müller et al., 2000) or treatment resistance (Lin et al., 1998), as the characteristics of deficit patients are similar to these correlates. A marginally statistical association between the severity of negative symptoms and a polymorphism of the IL6 gene (IL6-1 rs1800797) has also been described in schizophrenia (Liu et al., 2010). Some (Ganguli et al., 1994; Akiyama, 1999; Fernandez-Egea et al., 2009) but not all studies (Singh et al., 2009) have found an increased IL6 in drug-naïve patients. The described abnormality in each of these markers provides a degree of validation of the abnormality in the other.

Whether these abnormalities in cytokines are part of the pathophysiology or even etiology of schizophrenia, or a result of the stress associated with the disorder, is not known (Corcoran et al., 2003). Another complicating factor for many studies (although not the present study) is that antipsychotic treatment may also modulate the production of cytokines (Szuster-Ciesielska et al., 2004). Inflammation may prove to be an important target for the development of therapeutics, as some studies suggest they may increase the speed of recovery from a relapse (Müller et al., 2004, 2005, 2010; Bresee et al., 2006; Akhondzadeh et al., 2007; Laan et al., 2007).

We previously hypothesized that deficit schizophrenia is a separate disease within the syndrome of schizophrenia, based on studies that had shown that deficit and nondeficit schizophrenia differed with regard to signs and symptoms, risk factors, course of illness, biological correlates, and treatment response (Kirkpatrick et al., 2001). The current double dissociation in glucose tolerance and inflammation supports this hypothesis. Two other double dissociations have also been found. One is in event-related potentials: the N1 component has been found to be abnormal in deficit but not nondeficit patients, whereas the P3 component was affected only in nondeficit patients (Mucci et al., 2007). Another double dissociation is in season of birth: deficit schizophrenia is associated with summer birth (Messias et al., 2004) whereas schizophrenia as a whole (and therefore nondeficit schizophrenia) is associated with winter birth (Torrey et al., 1997).

Deficit and nondeficit patients have been found to have different risk factors, suggesting that these two groups have differences in etiopathophysiology. The metabolic differences we report here may therefore reflect differences in prenatal metabolic programming. Although replication would be needed, our present results support the hypothesis of a separate disease.

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