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Decreased glutathione levels predict loss of brain volume in children and adolescents with first-episode psychosis in a two-year longitudinal study

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ABSTRACT

Progressive loss of cortical gray matter (GM), as measured by magnetic resonance imaging, has been described early in the course of first-episode psychosis. This study aims to assess the relationship between oxidative balance and progression of cortical GM changes in a multicenter sample of first-episode early-onset psychosis (EOP) patients from baseline to two-year follow-up.

A total of 48 patients (13 females, mean age 15.9 ± 1.5 years) and 56 age- and gender-matched healthy controls (19 females, 15.3 ± 1.5 years) were assessed. Magnetic resonance imaging (MRI) scans performed both at the time of the first psychotic episode and 2 years later were used for volumetric measurements of left and right gray matter regions (frontal, parietal, and temporal lobes) and total sulcal cerebrospinal fluid (CSF). Total glutathione (GSH) blood levels were determined at baseline.

In patients, after controlling for possible confounding variables, lower baseline GSH levels were significantly associated with greater volume decrease in left frontal ($B = 0.034$, 95% confidence interval (CI): 0.011 to 0.056, $r = 0.620$, $p = 0.006$), parietal ($B = 0.039$, 95% CI: 0.020 to 0.059, $r = 0.739$, $p = 0.001$), temporal ($B = 0.026$, 95% CI: 0.016 to 0.036, $r = 0.779$, $p < 0.001$), and total ($B = 0.022$, 95% CI: 0.014 to 0.031, $r = 0.803$, $p < 0.001$) gray matter, and with greater increase in total CSF ($B = -0.560$, 95% CI: −0.270 to −0.850, $r = -0.722$, $p = 0.001$). Controls did not show significant associations between brain volume changes and GSH levels. GSH deficit during the first psychotic episode was related to greater loss of cortical GM two years later in patients with first-episode EOP, suggesting that oxidative damage may contribute to the progressive loss of cortical GM found in patients with first-episode psychosis.

1. Introduction

There is a strong evidence that subjects at ultra-high risk for psychosis (Sun et al., 2009; Takahashi et al., 2009), children and adolescents with early-onset psychosis (EOP) (Arango et al., 2008, 2012; Rapoport et al., 1999; Reig et al., 2009a), and adults with first-episode schizophrenia (Koo et al., 2008; Mane et al., 2009) show a progressive loss of gray matter (GM) volume in the initial years after symptom onset compared with healthy controls. The mechanisms underlying this progressive loss of GM volume are unclear but probably comprise genetic (Gogtay, 2008; Rijsdijk et al., 2005; Styner et al., 2005) and environmental factors (Ho et al., 2003; Steen et al., 2006).

A final common feature of brain cell damage is oxidation of cell components, which occurs when pro-oxidant/antioxidant balance is displaced to the left (Wood et al., 2009). There is an increasing interest in the pathophysiological role of antioxidant status in schizophrenia spectrum disorders (van Os et al., 2010). An impaired antioxidant defense system has been reported in patients with schizophrenia and their siblings (Ben Othmen et al., 2008; Bitanihirwe and Woo, 2011; Wang et al., 2009; Yao and Keshavan, 2011). Glutathione (GSH) is one of the main cellular non-protein antioxidants and redox regulators, and it constitutes

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the major free radical scavenger in the brain. Hence, diminished GSH levels elevate cellular vulnerability to oxidative stress (Gawryluk et al., 2011), and decreased GSH levels have been reported in studies using animal models of schizophrenia as well as post-mortem studies of the prefrontal cortex in patients with major psychiatric disorders (such as schizophrenia or bipolar disorder) (Dean et al., 2009; Gawryluk et al., 2011; Radonjic et al., 2010).

Recently, our group showed that, compared with controls, schizophrenia patients had greater GM volume loss in the frontal lobe and greater frontal CSF volume increase over a two-year follow-up period (Arango et al., 2012). Additionally, our group found a decrease in GSH in patients with first-episode EOP compared with controls, suggesting that decreased GSH levels may contribute to the pathophysiology of EOP (Micó et al., 2011). Taking both results together, it may be hypothesized that the loss of brain volume found at early stages of first-episode psychosis is related to GSH levels.

The purpose of the present study was to assess whether there is a relationship between GSH levels and progression of cortical GM volume loss as measured by MRI in a multicenter sample of first-episode EOP patients, compared with age- and gender-matched healthy controls, over a 2-year follow-up period. The underlying hypothesis was that lower levels of antioxidant markers would be positively related to greater MRI brain volume deficits in EOP.

2. Materials and methods

2.1. Subjects

A total of 48 first-episode EOP patients and 56 age- and gender-matched healthy controls formed the study sample. All subjects in this study were participants in the longitudinal Child and Adolescent First-Episode Psychosis Study (CAFEPS) (Castro-Fornieles et al., 2007). The CAFEPS comprised a total of 110 patients with first-episode psychosis (FEP) and 98 healthy controls matched for age, gender, and parental socioeconomic status. The sample was consecutively recruited in out- and in-patient units at 6 hospitals in Spain (2 in Madrid, 1 in Barcelona, 1 in Santander, 1 in Vitoria, 1 in Pamplona). Recruitment took place between March 2003 and 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. The exclusion criteria were 1) concomitant Axis I disorder at the time of evaluation, 2) mental retardation according to DSM-IV criteria, 3) any neurological or pervasive developmental disorder, 4) history of head trauma with loss of consciousness, 5) pregnancy, and 6) substance abuse or dependence but not use if psychotic symptoms persisted 14 days after a negative urine drug test.

The diagnosis was confirmed according to the DSM-IV-TR criteria using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997), Spanish translation (Soutullo, 1999), at the 2-year follow-up evaluation. Healthy controls were selected from publicly funded schools with characteristics similar to those attended by patients in the community through advertisements and from among children who were seen for routine pediatric visits at our hospitals, all from the same geographic areas as the healthy controls. The inclusion criteria for controls were age and sex similar to the patients, coming from the same geographical areas as the patients, no psychiatric disorder as measured by the K-SADS-PL, and no neurological disorders, head trauma, pregnancy, or mental retardation (again per DSM-IV criterion).

At the time the study was conducted, the adolescent psychiatric units of our hospitals were the referral departments for children and adolescents with psychosis for all the regions involved in this study. As hospitalization is the general rule for a psychotic episode in children and adolescents, and there were no private facilities for hospitalizing children and adolescents in the catchment areas of these hospitals, we believe that our study sample is representative of EOP.

Of the entire sample (controls and patients) enrolled in the CAFEPS, magnetic resonance imaging (MRI) scans at baseline and at the two-year follow-up and oxidative stress data at baseline were available for a total of 48 patients and 56 age- and gender-matched healthy control subjects. Fig. 1 shows a diagram of subjects eligible for this study.

WISC-R or WAIS-III vocabulary and block tests were used to estimate intelligence quotient (IQ) of patients and controls under or over 16 years of age, respectively (Satler, 2001). Data on tobacco abuse or dependence (as a dichotomous yes/no variable according to DSM-IV criteria) during follow-up, mean daily dose of antipsychotic treatment during the two-year follow-up (in chlorpromazine equivalents) (Andreasen et al., 2010; Rijcken et al., 2003), and length of illness prior to baseline brain image acquisition were also collected.

The study was approved by the ethics and clinical research boards of all hospitals involved in the study. After receiving a complete explanation of the study, parents or legal representatives gave written informed consent; participants under the age of 12 assented to participate in the

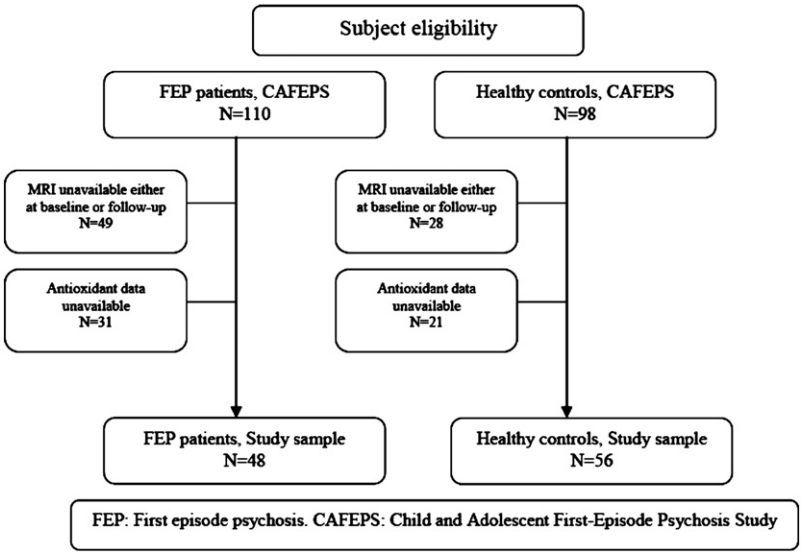

Fig. 1. Subject eligibility.