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OXIDATIVE STRESS AND BRAIN VOLUMES IN EARLY ONSET PSYCHOSIS: ROLE OF DECREASED GLUTATHIONE LEVELS IN PROGRESSIVE LOSS OF CORTICAL GREY MATTER.

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INTRODUCTION

- Progressive loss of cortical gray matter (GM) has consistently been reported in patients with first-episode psychosis [1].
- An altered antioxidant defense system has been reported in patients with schizophrenia and their siblings [2].
- Glutathione (GSH) is one of the main cellular non-protein antioxidants and redox regulators, constituting the major free radical scavenger in the brain.
- Recently, our group found a decrease in antioxidant defense (specifically in GSH) in patients with first-episode EOP compared to controls, suggesting that oxidative damage is present in these patients, and may contribute to the psychosis pathophysiology [3].
- Thus we hypothesized that brain volume changes found at early stages of first-episode psychoses are related to levels of GSH.

OBJECTIVES

- 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 at two-year follow-up.

METHODS

- A sample 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) using automated method based in Talairach´ atlas.
- At baseline total antioxidant status (TAS), and lipid peroxidation were determined in plasma. Enzyme activities (catalase, glutathione peroxidase, and superoxide dismutase) and total glutathione (GSH) levels were determined in erythrocytes.
- Multiple linear analysis (general linear model, MANCOVA/OLS) was used to assess the association between oxidative/antioxidant markers and brain volumes changes controlling for age, gender, smoking status, psychopathology, mean accumulative antipsychotic dose, length of illness at MRI, and comparison group (schizophrenia & schizoaffective disorder (n=27), bipolar disorder (n=12), and other psychoses (n=9)).
- We conducted two separate multivariate analyses: 1) for patients (using the previous confounders) and 2) for controls (controlled for age, gender, smoking status, and race). In order to analyze the relationship between oxidative stress markers and changes on brain volumes during the two-year follow-up, arithmetic change values (2-year volume minus baseline volume) were obtained for each of the a priori hypothesized regions, adjusting for multiple-comparisons by a Bonferroni correction.

RESULTS

RELATIONSHIP BETWEEN BASELINE OXIDATIVE STRESS MARKERS AND BRAIN VOLUME CHANGES IN FIRST EPISODE EOP PATIENTS ±

	TAS	GSH
Change in left frontal GM volume	r=0.337, F=1.79, p=0.202	r=0.620, F=8.75, p=0.010
Change in left parietal GM volume	r=0.339, F=2.65 , p=0.126	**r=0.739, F=16.84, p=0.001**
Change in left temporal GM volume	r=0.146, F=0.31, p=0.590	**r=0.779, F=21.66, p<0.001**
Change in right frontal GM volume	r=0.262, F=1.03, p=0.326	r=0.076, F=0.81, p=0.780
Change in right parietal GM volume	r=0.133, F=0.25, p=0.625	r=0.046, F=0.29, p=0.866
Change in right temporal GM volume	r=0.336, F=1.78, p=0.204	r=0.006, F=0, p=0.984
Change in total sulcal CSF volume	r=0.255, F=0.976, p=0.340	**r=0.722, F=15.22, p=0.002**

±Two multivariate analyses (general lineal model) were conducted (for TAS and GSH). Analyses included brain volumes as dependent variables, and baseline GSH/TAS levels, age (at baseline), gender, baseline smoking status (as dichotomous variable yes/no), psychopathology (as baseline positive, negative and general PANSS scores), mean daily antipsychotic dose during the follow-up (as chlorpromazine equivalents), days of length of illness up to baseline brain image acquisition, race and comparison group (schizophrenia & schizoaffective disorder, bipolar disorder, and other psychoses) as covariables.
CPZ: chlorpromazine. CSF: cerebrospinal fluid. EOP: early onset psychosis. GM: gray matter. TAS: Total antioxidant status. GSH: Glutathione. r= partial correlation (controlled for the specified variables).
Significant values (p<0.0036, after Bonferroni correction) are in boldface.

- **Among patients, after controlling for possible confounding variables, baseline lower GSH levels were significantly associated with greater volume decrease in parietal (r=0.739, p=0.001) and temporal (r=0.779, p<0.001) left gray matter, and with greater increase of total CSF (r=0.722, p=0.002).**
- **Controls did not show significant associations between brain volume changes and oxidative/antioxidant markers (table 1).**

CONCLUSIONS

- **GSH deficit measure during the first psychotic episode is related with 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.**

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