Schizophrenia Research 156 (2014) 23–29

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Basal low antioxidant capacity correlates with cognitive deficits in early onset psychosis. A 2-year follow-up study

Mónica Martínez-Cengotitabengoa [a,b,c,*], Juan Antonio Micó [b,d], Celso Arango [b,e,f], Josefina Castro-Fornieles [b,g,h], Montserrat Graell [i], Beatriz Payá [j], Juan Carlos Leza [b,k], Iñaki Zorrilla [a,b], Mara Parellada [b,e], Mª. Purificación López [a,b,l], Inmaculada Baeza [m], Carmen Moreno [b,e], Marta Rapado-Castro [b,e], Ana González-Pinto [a,b,l]

[a] Department of Psychiatry, Hospital Universitario de Alava, Vitoria, Spain
[b] Centro de Investigación Biomédica en Red de Salud Mental — CIBERSAM, Instituto de Salud Carlos III, Madrid, Spain
[c] National Distance Education University (UNED)-Centro Asociado de Vitoria, Spain
[d] Neuropsychopharmacology and Psychobiology Research Group, University of Cadiz, Cadiz, Spain
[e] Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, IiSGM, Madrid, Spain
[f] Medical School, Universidad Complutense, Madrid, Spain
[g] Department of Child and Adolescent Psychiatry and Psychology, SGR-1119, Neurosciences Institute, Hospital Clinic, IDIBAPS, Barcelona, Spain
[h] Department of Psychiatry and Psychobiology, University of Barcelona, Spain
[i] Department of Child and Adolescent Psychiatry and Psychology, University Hospital Niño Jesús, Madrid, Spain
[j] Child and Adolescent Psychiatry and Psychology Unit, University Hospital Marques de Valdecilla, Santander, Spain
[k] Department of Pharmacology, Medical School, Universidad Complutense, Madrid, Spain
[l] University of the Basque Country, Spain
[m] Department of Psychiatry, Clinic Institute of Neurosciences, Hospital Clinic, Barcelona, Spain

ARTICLE INFO

Article history:
Received 13 November 2013
Received in revised form 7 February 2014
Accepted 25 March 2014
Available online 24 April 2014

Keywords:
First episode
Psychosis
Oxidative stress
Cognition
Non-affective psychosis

ABSTRACT

The objective of the study is to examine the association of baseline total antioxidant status (TAS) and glutathione (GSH) levels with short- and long-term cognitive functioning in patients with early onset first-episode psychosis, comparing affective and non-affective psychoses.

We analysed 105 patients with an early onset-first episode psychosis (age 9–17 years) and 97 healthy controls. Blood samples were taken at admission for measurement of TAS and GSH, and cognitive performance was assessed at baseline and at 2 years of follow-up. Regression analysis was used to assess the relationship between TAS/GSH levels at baseline and cognitive performance at both time points, controlling for confounders.

Baseline TAS and GSH levels were significantly lower in patients than healthy controls. In patients, baseline TAS was positively associated with the global cognition score at baseline ($p = 0.048$) and two years later ($p = 0.005$), while TAS was not associated with cognitive functioning in healthy controls. Further, baseline TAS in patients was specifically associated with the memory domain at baseline and with the memory and attention domains two years later. Stratifying by affective and non-affective psychoses, significant associations were only found between TAS and cognition in the non-affective psychosis group. Baseline GSH levels were not associated with cognitive functioning at either time point in either group.

The antioxidant defence capacity in early onset first-episode psychotic patients is directly correlated with global cognition at baseline and at 2 years of follow-up, especially in non-affective psychosis.

1. Introduction

An imbalance between pro-oxidant and antioxidant mechanisms in cells is thought to play a role in the pathophysiology of many diseases of the central nervous system, such as schizophrenia (Fendri et al., 2006; Bitanihirwe and Woo, 2011). As this imbalance is a potential cause of oxidative stress and damage to key brain circuits (van Os et al., 2010; Andreazza, 2012; Anderson et al., 2013) the accumulation of pro-oxidant molecules (i.e., reactive oxygen species) and/or impaired anti-oxidant defence mechanisms (both enzymatic and non-enzymatic) have become targets for study in psychotic disorders. The interest in and the evidence to justify these studies come from previous research

* Corresponding author at: CIBERSAM-Psychiatry Research Unit, University Hospital of Alava, Calle Olaguibel 29, 01004 Vitoria, Spain. Tel./fax: +34 945 007764.
E-mail address: monica.martinezcengotitabengoa@osakidetza.net (M. Martínez-Cengotitabengoa).

http://dx.doi.org/10.1016/j.schres.2014.03.025

Table 1
Neuropsychological tests and variables grouped by cognitive domain.

Cognitive domain	Neuropsychological variable
Attention	WAIS-III[a] Digits Forward
	Time to complete TMT-A[b]
	Number of correct items, Stroop 1 words
	Number of correct items, Stroop 2 colours
	Number of correct responses, CPT[c]
	Average reaction time, CPT
Working memory	WAIS-III Digits Backward
	WAIS-III Number–Letter Sequencing
Learning and memory	TAVEC[d] Total Learning
	TAVEC Short Term Free Recall
	TAVEC Long Term Free Recall
	TAVEC Discrimination
Executive functions	Time to complete TMTB[e]
	Number of words, FAS[f]
	Number of words, COWAT[g]
	Stroop Interference score
	WCST[h] number of perseverative errors
	WCST number of errors
	WCST conceptual level responses

[a] WAIS-III: Wechsler Adult Intelligence Scale, 3rd edition (Wechsler, 1997).
[b] TMT-A: Trail Making Test, part A (Spreen and Strauss, 1998).
[c] CPT: Conners' Continuous Performance Test (Conners, 2000).
[d] TAVEC: Spanish version (Benedet et al., 2001) of the California Verbal Learning Test (Delis et al., 1994).
[e] TMTB: Trail Making Test, part B = (time to complete TMT-B − time to complete TMT-A) / time to complete TMT-A (Spreen and Strauss, 1998).
[f] FAS: Verbal fluency test (Spreen and Strauss, 1998).
[g] COWAT: Control Oral Word Association Test. Semantic category "animals" (Benton, 1994).
[h] WCST: Wisconsin Card Sorting Test (Heaton, 1981; Spreen and Strauss, 1998).

in both adults (Anderson et al., 2013), children (Micó et al., 2011), and their siblings (Ben Othmen et al., 2008).

In the search for biomarkers of functional or structural damage in psychiatric disorders, early studies have suggested that total antioxidant status (TAS) should be systematically measured given its association with the pathophysiology of schizophrenia spectrum disorders (Ustundag et al., 2006). TAS reflects the cumulative effects of all antioxidants present in the plasma and other body fluids. Studies measuring TAS have found lower levels of antioxidants in patients with neuropsychiatric diseases (such as schizophrenia and bipolar disorder) than in healthy controls (Micó et al., 2011), as well as a dysfunctional balance of oxidative and pro/anti-inflammatory pathways in first-episode psychosis (FEP) (García-Bueno et al., 2013). It is especially important to study the disease at its outset as it is possible to find pathophysiological clues uncontaminated by chronicity or drug effect (Bernardo et al., 2013).

It is also of relevance to psychosis that oxidative stress can promote macro and microglial damage, including axonal demyelination (Qin et al., 2008; rev. in Adibhatla and Hatcher, 2010). Indeed, it has recently been shown that lower baseline plasma levels of the main cellular antioxidant, glutathione (GSH) at the time of a first psychotic episode are associated with greater decreases in cortical grey matter two years later in patients with early onset psychosis (Fraguas et al., 2012), suggesting a role for oxidative damage in the pathophysiology of this disease.

The relationship between oxidative stress and cognition has been explored in some studies. In a previous study of adults with FEP, we found that plasma GSH levels were positively associated with executive functioning (Martinez-Cengotitabengoa et al., 2012). A recent study found that higher activity of plasma manganese superoxide dismutase (a mitochondrial enzyme that detoxifies superoxide radicals to hydrogen peroxide) was significantly correlated with the degree of cognitive impairments in patients with schizophrenia (Zhang et al., 2013). Although these findings support an association between oxidative stress and cognitive deficits, both studies were cross-sectional in design and, to our knowledge, there have been no longitudinal studies.

The objective of this study was to explore the long-term effects of low baseline TAS and GSH levels on the cognitive functioning of patients with early onset psychosis. We hypothesized that the antioxidant status of patients during an early first psychotic episode would be inversely associated with their cognitive performance at baseline and two years after the acute episode. Further, for this analysis, we stratified patients into those with affective and non-affective psychoses.

2. Methods

2.1. Subjects

The original Child and Adolescent First-Episode Psychosis Study (CAFEPS) was a case–control study that included 110 FEP patients aged 9–17 years at the time of first evaluation. A first episode of psychosis was defined as the presence of positive psychotic symptoms of delusions or hallucinations for a period of less than 6 months. This short duration of symptomatology was used to obtain a more homogenous patient sample. Patients were recruited from Child and Adolescent Psychiatry Units at six university hospitals in Spain. Sample recruitment and patient characteristics have been described elsewhere (Castro-Fornieles et al., 2007). Exclusion criteria were: the presence of any other Axis I disorder that might account for the psychotic symptoms (such as substance abuse, autistic spectrum disorders, post-traumatic stress disorder, and acute stress disorder); mental retardation according to DSM-IV criteria, including not only an intelligence quotient of less than 70, but also impaired functioning; pervasive developmental disorder; neurological disorders; a history of head trauma with loss of consciousness; and pregnancy. Patients were not excluded for occasional substance use if positive symptoms persisted for more than two weeks after a negative urine drug test.

The study also included 98 healthy control subjects who were selected from the same catchment area and matched to the patients by age and gender. They were selected from publicly-funded schools with similar characteristics to those attended by patients through advertisements and from children who were seen for routine paediatric visits at our hospitals. The control subjects had no history of Axis I psychiatric disorders, neurological disorders, mental retardation, or head trauma, and were not pregnant, and there was no history of psychiatric disorders in their first-degree relatives.

Baseline blood samples for measuring oxidative stress were available for 105 patients and 97 controls of the original sample and these individuals were included in the present analysis. The study was approved by the Ethics and Clinical Research Boards of all the hospitals involved in the study. Parents or legal guardians gave written informed consent and patients assented to participate in the study.

2.2. Design and clinical assessment

In this prospective study, we assessed the antioxidant status of FEP patients at baseline and evaluated their cognitive functioning at baseline and two years later.

All patients met the DSM-IV criteria for a FEP (American Psychiatric Association, 1994), assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). Clinical assessments on admission and two years later were performed by an experienced child psychiatrist with specific training in the K-SADS-PL semi-structured interview. Socioeconomic status was estimated using the Hollingshead and Redlich scale (Hollingshead and Redlich, 1958), administered to the parents by the same clinician.

2.3. Oxidative stress evaluation

Based on preliminary data (Micó et al., 2011), we focused the present analyses on the following oxidative variables: TAS as a global measure of