Author's response to reviews

Title: Antioxidant defense system and family environment in adolescents with family history of psychosis

Authors:

ANA GONZALEZ-PINTO (anamaria.gonzalez-pintoarrillaga@osakidetza.net)
MONICA MARTINEZ-CENGOTITABENGOA (monica.martinezcengotitabengoa@osakidetza.net)
CELSO ARANGO (carango@hggm.es)
IMMACULADA BAEZA (ibaeza@clinic.ub.es)
SORAYA OTERO-CUESTA (soteroc@intersep.org)
MONTSERRAT GRAELL-BERNA (mgraellb@terra.com)
CESAR SOUTULLO (csoutullo@unav.es)
JUAN CARLOS LEZA (jcleza@med.ucm.es)
JUAN ANTONIO MICO (Juanantonio.mico@uca.es)

Version: 2 Date: 12 July 2012

Author's response to reviews: see over
Reviewer's report

Title: Antioxidant defense system and family environment in adolescents with family history of psychosis
Version: 1 Date: 29 April 2012
Reviewer: Anwar Mechri
Reviewer's report:

The title and abstract accurately convey what has been found. The writing is acceptable. However, the question posed by the authors is not well defined and has not been argued. The methods are well described, but have serious limitations. Some conclusions are not adequately supported by the data of this study.

Minor revisions:

- Please correct the first references citation in the introduction line 4
  Corrected
- Third paragraph of introduction should be referenced: …"All of these species have been found altered in schizophrenic patients”.

We have referenced this sentence with 3 articles:


- The objective of the study is not well formulated at the end of the introduction.

We have changed the paragraph describing the objective of the study to the following:

“The objectives of this study are to determine antioxidant defence at the peripheral level in healthy subjects with a family history of psychosis and to compare it with that of healthy people without affected relatives. We also examine the association between oxidative stress and familiar environment.”

Major revisions:

In the introduction:
The importance of the measurement of the antioxidant defense in unaffected relatives of early onset psychosis patients is not mentioned. Similarly, the rationale of the assessment of relationship between antioxidant defense and the familiar environment is not presented. Why the authors suggested that family environment may induce oxidative stress in healthy subjects? The rational for this hypothesis should be formulated.

We have described the rationale and hypothesis of our study by including the following new paragraph in the text:

“Results from animal models have shown that poorer environmental conditions are associated with more oxidative stress [Bourgeon et al, 2011], and this is probably due to the need to transfer energy towards processes with a high energy cost, such as immune function, antioxidant defence and DNA repair processes [Nilson et al 2002]. The relationship between environmental conditions and oxidative stress has not been examined in healthy humans. In a previous study, we have shown that antioxidant defence is decreased in children and adolescents with early onset first-episode psychosis [Mico et al, 2011]. If environmental factors play a role in this, antioxidant defence may also be decreased in the unaffected relatives of such patients. Our hypothesis is that healthy control subjects with a family history of psychosis will have a lower antioxidant capacity than healthy subjects without this family history, and that the antioxidant capacity will be modulated by environmental family factors.”

In the methods:

The design of the study is not clear; all subjects were controls in previously study. A small number of them (n = 14) had second degree relatives with psychotic disorders, but there is no certainty that other subjects had not family history of psychiatric disorders.

In the “Methods” section we explain that healthy subjects with first-degree relatives with psychosis were excluded from the study. We also describe that an interview was conducted to determine the family history of psychosis in up to third-degree relatives. Thus, we are certain that the HC group had no family history of psychosis. The HC-FHP group had second-degree relatives with psychosis.

The differences can be explained by the small group size (HC-FHP) with the risk of under or over estimate.

Statistical analyses were done to exclude type II errors. Nevertheless, in the study limitations sections we have mentioned that the small sample size may obscure some of the associations found.

In the discussion and conclusion:
The hypothesis “that families with relatives of psychosis protect themselves with positive environmental factors such as cohesion and intellectual-cultural activities” is based solely on the existence of a difference with a small group size. I think that this conclusion can not be justified by these results.

This conclusion is based on the results with a small sample and further studies are certainly warranted. We have mentioned this as a limitation of the study.

Level of interest: An article of limited interest  
Quality of written English: Acceptable  
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.  
Declaration of competing interests:  
I declare that I have no competing interests.
Reviewer's report

Title: Antioxidant defense system and family environment in adolescents with family history of psychosis
Version: 1 Date: 8 May 2012
Reviewer: Stephen Wood
Reviewer's report:

The authors present an interesting but limited study which shows a significantly lower total antioxidant level in the blood of young people who have a second degree relative with psychosis, when compared to group without such family history. The finding seems secure, and potentially important. Of course, it would be better if the authors had information about people more closely related to people with psychosis, but this seems to be a useful addition to the literature nonetheless.

Major Compulsory Revisions

The main issue I have with the manuscript as submitted is that the introduction does not usefully guide the reader as to the purpose of the study. It is only once one is well into the methods section that it is apparent that a) there are no patients in this study and b) that the family history group is 2nd degree and a sample of convenience.

The introduction also gives no background as to the role of genetics or family history in oxidative biology, either in schizophrenia or healthy subjects.

We have clarified in both the abstract and introduction that this study is in healthy subjects with and without a family history of psychosis.

We have included the following paragraph in the introduction:

“Oxidative stress levels are influenced by various factors, including genetics. It has been shown that antioxidant capacity could have a genetic basis [Mosconi et al, 2010, Zengi 2011, Kim 20101], which would be modified throughout life by environmental factors [Metcalf 2001], suggesting the possible presence of an early dysfunction in the antioxidant defence system in genetically predisposed individuals [Madec 2011].”

Minor Essential Revisions

I recommend that the authors reread (or get a native English speaker to read) the text to tighten up the grammar and remove some clumsy sentences that impede the reader's understanding.
I think it would be useful to include tobacco use in Table 1, since the authors clearly have the data and they are highly relevant to oxidative stress. Tobacco consumption data have been included in table 1.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests

Reviewer's report
Title: Antioxidant defense system and family environment in adolescents with family history of psychosis
Version: 1 Date: 2 May 2012
Reviewer: Murat Kuloglu

Reviewer's report:

It is an interesting article that attempted to associate causal relationship between the antioxidant defense system of second degree relatives of first episode psychotic patients and healthy subjects. It is a very different and interesting approach that will able to demonstrate the vulnerability to psychosis on a robust biological basis. However there are some issues which should be identified.

Firstly, I think that number of cases is small for comparing healthy subjects.

We agree with this comment, therefore, we have included the small study sample as a limitation of our study.

I also suggest that authors should demonstrate the correlation results on tables.

Thank you for the suggestion. We have included OR data in tables 2 and 3.

Authors include psychotic disorder not otherwise specified, schizophreniform disorder, depressive disorder with psychotic symptoms, bipolar disorder, schizophrenia, schizoaffective disorder and other psychotic disorders into first episode psychosis. However, the genetic background varies between-at least- mood disorders and schizophrenia. If there is a similarity in terms of antioxidant defence
system between these disorders that were included, authors should discuss this in introduction.

We have explored the neurobiology of oxidative stress in healthy controls and in healthy controls with relatives who have first episode psychosis as a whole group without making any difference between diagnoses due to the sample size, because we consider that the sample size is not large enough for subdivisions according diagnosis. Nevertheless, it has been widely assessed that there is an imbalance between antioxidant defence and oxidative attack in the first time a patient has a psychotic episode.

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: 'I declare that I have no competing interests'