Reviewer's report

Title: Familial liability, obstetric complications and childhood development abnormalities in early onset schizophrenia: a case control study

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Reviewer: Marco Picchioni

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Margari et al; FAMILIAL LIABILITY, OBSTETRIC COMPLICATIONS AND CHILDHOOD DEVELOPMENT ABNORMALITIES IN EARLY ONSET SCHIZOPHRENIA: A CASECONTROL STUDY

Thank you for asking me to review this paper. It explores the experimental hypothesis that genetic (family history) and environmental risk factors for schizophrenia are over represented in an early/very early onset schizophrenia sample.

The strengths of this study are:
-its basis within a Child & Adolescent Clinical Neuropsychiatry Service
-the relatively large number of subjects with a rare disorder

The weaknesses are:
-the lack of a more informative contrast sample
-the small number of observations in some cells

Major Essential

Abstract:
While the title talks of familial liability, the body of the text talks more of genetic risk. The design of the study prevents it from being able to make any conclusions about genetic risk.

Background:
The first paragraph advances the hypothesis that E/VEOS are associated with a greater genetic and environmental aetiological load, though the authors do not say in relation to what? Is it in relation to the adult form of the illness? What some of the results show is that E/VEOS is associated with some of the risk factors that are thought to be are associated with schizophrenia to a greater extent than hemicrania.

What would have been much more interesting is to establish whether, in addition E/VEOS are associated with these factors more than the adult onset form of the illness. Parts of the Background section appear to advance this hypothesis, yet this is not addressed by the design of the study.

I recognise the advantage that all the subjects assessed were children and that
hypothetically they, or their parents, would be prone to less recall error.

Surely the central question is whether the hypothetical 'schizophrenia' risk factors, family history (genetic & shared environmental risk), obstetric complications (environmental risk) and markers of aberrant early neurodevelopment, are more often found in E/VEOS than the adult onset disorder, rather than a non-psychiatric disorder control group? Or perhaps to compare E v VEOS, though I recognise that the numbers so far recruited are too small.

Methods:

I am not a statistician but for chi-square tests, we often work to the rule that each cell should have a minimum of 5. This doesn't seem to be the case from my reading of the tables. A statistical opinion would help to clarify?

Results:

I don't think tables 2 and 3 need to be separate, while I find table 2 confusing. It seems, if I am reading the tables correctly that the numbers are inconsistent between the two. Table 2 lists the complication rates as: Prepartum 90% Peripartum 55% Postpartum 36% in the E/VEOS group. Table 3 lists Prepartum 10 (50%) Peripartum 6 (30%) Postpartum 4 (20%). If I am misreading it I apologise, but the labelling is then unclear.

Discussion & Conclusion

The design of this study can go no further than commenting that there is a familial aspect to E/VEOS schizophrenia. Any interpretation that this is genetic, rather than shared environment is speculation from this data. The authors should reflect this uncertainty.

The nature of the personality pathology in the relatives is not described, the authors over interpret the data, while again overstating the genetic case.

The authors spend most of the paragraph about OCs overstating their aetiological role, only highlighting the uncertainty about their aetiological role in schizophrenia in the last sentence.

Minor Essential

Abstract

The general 'readability' of this paper needs to be improved. Furthermore there are typos in the text and tables throughout.

The choice of the term 'remarkable' is hard to justify.

Background

I suggest dropping the term 'precocious' in relation to OCs.

The authors can be more explicit about their hypotheses.

I think it is best for the authors to avoid saying, even if risk factors were found with increased frequency in the E/VEOS, that the study verifies that they increase the risk for the illness. The study is retrospective and the statistics employed
correlations, these are associations.

Methods:
To what degree of relative was the family history assessed? This is missing from
the text?

Given that these patients were children and the researchers were in contact with
the respective parents, getting the obstetric records to validate the OC data,
would be a strength. This should be acknowledged as a limitation.

Results
The term patient is used to describe those with E/VEOS, though both groups are
patients and were recruited from clinical services, at other points cases and
controls is used.

The demographics and clinical features would be more easily presented in a
table. The detailed description of the prodromal phase and symptomatology of
the illnesses seem unnecessary, assuming the diagnosis of schizophrenia is
robust. Were the symptoms described current or lifetime?

Is gestational age > 37 weeks a typo?

Since DSM criteria were used for the diagnosis of schizophrenia I suggest
sticking to DSM terms in relation to IQ as well.

No details of the e.g. IQ or EEG results are given for the control group, though
earlier in the methods it says both groups were assessed using the same
techniques.

In the reporting of the familial liability data section, I do not understand the last
sentence, I do no think the authors mean ‘emphasized’ or ‘referred’?

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: Yes, but I do not feel adequately qualified to assess the
statistics.

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