Author's response to reviews

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

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Author's response to reviews: see over
Dear Editor

I send you the revised manuscript FAMILIAL LIABILITY, OBSTETRIC COMPLICATIONS AND CHILDHOOD DEVELOPMENT ABNORMALITIES IN EARLY ONSET SCHIZOPHRENIA: A CASE-CONTROL STUDY by Margari F. et al, for eventual publication on your Journal as research article.

In accordance with editorial request the manuscript was revised following the directions of both reviewers; the parts of the text changed are highlighted in red. Were also made some language corrections to improve written english.

Follows a detailed description of the revisions made

Abstract:

Reviewer 1
Major Essential
• 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.

Minor Essential
• The choice of the term ‘remarkable’ is hard to justify.

Reviewer 2
• Please change to “The aim was to assess................. done
• Last sentence the abstract: correct the spelling of desease to disease. Done

Background
Reviewer 1

Major Essential

• 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?

  Was added: than the adult onset 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 vs VEOS, though I recognise that the numbers so far recruited are too small.

  We all agree with your remarks, at any rate literature lacks comparative studies between EOS/VEOS and AOS. The available data on family history of psychiatric disorders, obstetric complications, childhood neurodevelopmental abnormalities in EOS/VEOS patients are mostly compared to formerly published data on adult onset patients. Moreover, when the information on risk factors for schizophrenia results from retrospective studies on small samples, recall errors could make data between young and adult patients less comparable. Our research activity pivots currently on child and adolescents patients; therefore in our present study reference was made to already published data on adult onset schizophrenia. We fully agree on that the central question is whether schizophrenia risk factors are more often found in E/VEOS than the adult onset disorder, hence during the last few months we have begun collecting data on AOS subjects too, thanks to the cooperation of the Psychiatric Unit; we are waiting to compare the data on numerically wider study groups.

Minor Essential

• 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.

  The second part of the background has been changed as follows:

  In the present study we examined a sample of 21 patients with EOS and VEOS; the control group was made up of 21 non-psychiatric patients affected by hemicrania, supposed to have a different pathogenesis for the illness; comparison was made according to age and gender. The aim of the study was the following:
1. To carry out a retrospective analysis of the frequency and typology of familial liability for psychiatric disorder, obstetric complications and childhood developmental abnormalities in the cases and controls;
2. To verify statistical association between EOS/VEOS and familial and environmental risk factors and childhood developmental abnormalities with respect to the control group.

Reviewer 2
- Second paragraph, second line change Than to then done
- Last line change to children and adolescents (add s) for children and adolescents
- Last line: change to should be more recent AND more reliable thus and

Methods

Reviewer 1
Major Essential
- 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?

Statistical opinion: As reported in the method section, a Fischer test was performed too. This test was used when the value in the cell <5.

Minor Essential
- To what degree of relative was the family history assessed? This is missing from the text?
  Was added: both first and second-degree relatives
- 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.

Was modified: Information about these precocious environmental risk factors was collected by interviewing the parents and examining birth records. (at the beginning of the assessment it had been written that past clinical records had been reviewed, also including birth records).

Reviewer 2
Assessment:
- Fourth para: first line, change the spelling to disease. done

Results

Reviewer 1
Major Essential
- 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.
Actually, the labeling is unclear. In table 3 the percentage of pre-, peri-and postpartum complications concerns only EOS/VEOS subjects with history of obstetric complications.

Minor Essential

• 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 term patient has been all over replaced by cases and controls or, alternatively by EOS/VEOS subjects.

• 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?

The demographic features of cases and controls have been summarized in table 1

The description about the onset of the conlamed psychotic symptoms has been shortened. The description of prodromic phase has been cut off.

• Is gestational age > 37 weeks a typo?

Yes, it was. It has been corrected with age < 37 weeks

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

Done: Further to DSM criteria, assessment of the intelligence quotient showed that mild mental delay was present in 24% of the patients cases, while 9.5% had a borderline IQ.

• 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.

We made clear that in the control group no IQ/EEG/MRI pathological data were found.

• In the reporting of the familial liability data section, I do not understand the last sentence, I do not think the authors mean 'emphasized' or 'referred'?

The term “Emphasized” has been replaced by “noted”

The term “referred” has been replaced by “were shown to affect” and “concerned”

Reviewer 2

Third para: first line: patients presented with nonspecific symptoms:
done

b) Familial liability third line change p value to 0.0074 (not 0.0074)
done

Discussion & Conclusion

Reviewer 1

Major Essential

• 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.
Our comment on familial aspect to E/VEOS schizophrenia have been changed as follows:

As reported in other studies on familial liability for schizophrenia, we found that EOS/VEOS is associated with a specific increase in family history for schizophrenia and related disorders as well as for personality disorders, rather than general psychopathology. Furthermore, the different psychopathological expression between first and second degree relatives suggests that we should widen our knowledge about the personality of EOS/VEOS parents. As matter of fact psychopathological traits such as suspiciousness, withdrawal, social avoidance, introversion, diffidence, flattened affectivity are likely to account for the phenotypical expression relevant to familial vulnerability to schizophrenia, characterized by both genetic and environmental factors (35,36).

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

Unfortunately, being the cases at our disposal too low, we have decided to exhibit the data on family history of psychiatric disorders into broader diagnostic categories, to avoid the breaking up of the information into very small numbers.

- 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.

We have tried to summarize the data in the literature, emphasizing the discrepancy between the various sources.

Looking forward to hearing from you, I send my kindest regards.

Best wishes
Lucia Margari