Author's response to reviews

Title: Thyroid Function in Clinical Subtypes of Major Depression

Authors:

Dr Konstantinos N. Fountoulakis (kfount@med.auth.gr)
Dr Apostolos Iacovides (kfount@med.auth.gr)
Dr Philippos Grammaticos (kfount@med.auth.gr)
Dr George S Kaprinis (kfount@med.auth.gr)
Dr Per Bech (gabean@fa.dk)

Version: 2 **Date:** 27 Dec 2003

PDF covering letter

Dear sir

I send you the revised MS Thyroid Function in Clinical Subtypes of Major Depression.
The manuscript was revised according to the recommendations of the referees.
More specifically

Reviewer No 1
Franco Benazzi Reviewer:

General
Interesting paper, important findings.
Discretionary Revisions (which the author can choose to ignore)
xxxxxxxx
Minor Compulsory Revisions (such as missing labels on figures, or the wrong use of a term, which
the author can be trusted to correct)
xxxxxxxx
Major Compulsory Revisions (that the author must respond to before a decision on publication can
be reached)
Introduction.
Please specifiy if unipolar or bipolar depression is the topic, it is unipolar MDD in the methods.
We have now included the term UNIPOLAR in several key places throughout the MS
Methods.
Given the small N of MDD, I would suggest not to split analyses according to subtypes.
Statistics: OK.
Results.
I would suggest not to split analyses according to MDD subtypes.
Well, you are probably right, but is study is only exploratory (we included it in the title) and thus, we think that it would be appropriate to keep this analysis. However we included a section 'advantages-disadvantages' at the end of the discussion in order to explain the restrictions because of the small study sample. As you note below, *'even if the sample is small, findings may open the way to larger studies increasing our insight into the relationship between thyroid and depression and treatment response'*
Discussion.
I would suggest to compact a lot, and to focus only on the main findings, which may have treatment impact.
The discussion was compacted
Given the small sample, I would stress the preliminary nature of the findings, needing replication in much larger samples.
The words : 'An exploratory study' were added in the title
I would suggest to make only 2-3 tables, without subdividing results according to MDD subtypes.

However, even if the sample is small, findings may open the way to larger studies increasing our insight into the relationship between thyroid and depression and treatment response.

We have focused on this issue above.

References.

I would suggest to reduce by 50%.

The references were reduced

Accept after minor compulsory revisions Advice on publication:

A paper whose findings are important to those with closely related research Level of interest:

interests

Acceptable Quality of written English:

Declaration of competing interests:

None

Reviewer No2

mauro giovanni G carta Reviewer:

General

Thyroid function in Clinical Subtypes of Major Depression

The paper deals with an interesting topic: the role of thyroid autoimmunity on psychopathological manifestations of symptoms of mood disorders and on the mood disorders outcome. Some methodological issues and the small sample size limit the relevance of the results. The authors should work on the style of the presentation.

Specific Remarks:

Introduction

The introduction seems not to clear or sufficiently focalized the importance of the topic, the starting hypothesis and its basis. The introduction should point out the recent hypothesis of a down regulation of hypothalamic-pituitary adrenal axis and CRH deficiency in atypical depression (see Gold PW and Chrouos GP, Mol Psychiatry 2002 7:254-75). As the modification of balance between proinfammatory and antiinflammatory cytokines may be related to cortisol and norepinefrine levels (see Elenkov et al. J Clin Metab 2001 86:4933-8, Elenkov and Chrousos Ann Acd Sci 2002 966:290-303) it is possible that only subtypes of depression are correlated with the autoimmune response. Besides, the comorbidity of other autoimmune syndromes as the celiac disease (Carta et al. J Psychosom Research 2002) with depressive episodes seems to be strictly correlated with the presence of thyroid autoimmunity.

The introduction section was rewritten and the suggested remarks and references were added

Methods

The measures of outcome are unclear. Authors write “According to their course during that period, they were divided in two groups….” Which are the positive outcome indicators? Symptoms at the end of the follow-up? Numbers of relapses/recurrences during the observation? The free periods of pathology?

Now, in the material we clearly say that the one group consisted of patients that manifested *‘full or almost full remission and no relapse during the whole 2 year period’* and the other of those *‘with partial attenuation of symptomatology without full remission or with relapses of episodes’*. We think it is clear now.

1) The study does not assess the anti-thyroid peroxidase autoantibodies (anti-TPO), why? They are considered the most sensitive and specific markers of thyroid autoimmunity (see Mariotti et al. J Clin Endocrinol Metab 1990;71:661-669).

The following phrase was included in the methods:

Although anti-TPO Ab assay by monoclonal antibody-assisted RIA appears to be more sensitive and specific for thyroid autoimmune diseases than other methods unfortunately it was not available in our laboratory at the time the study took place.

2) Statistical analysis: the sample size is at the limit of parametric tests applicability. It is difficult to accept that all thyroid parameters considered have a gaussian distribution (in contradiction against the hypothesis).

Well, again you are probably right. But given the exploratory nature of the study and the fact that the size is at the limit and does not clearly violate the rules we ask to accept this analysis

Results

Table 3 and 4: data correctly identify subtypes at 62%, 60%, 58.3% and controls at 98.3% but results are not statistically significant. This is also true for the distinction between treatment responders and not treatment responders. Authors should clarify these points.

We presume you mention the p-values below the discriminant analysis in tables 3 and 4. For example the p=0.008 below 'Undifferentiated' in table 3. If this is the case, this p-value stands for the comparison between observed vs. predicted values, and it is not significant because there is no difference between our data and the predicted by the discriminant function model for all functions (all subtypes). These p-values do not represent comparisons between groups. The fact that they imply non-significance is positive for the acceptance of the discriminant function analysis results.

There are clear differences between depressive subtypes detected by MANCOVA and mentioned in the results and tables 1 and 2.

Discussion

The conclusion that "melancholics are a more clearly defined and a core group" should be express with caution because of the methodological limits of the study.

A comment was added at the end of discussion

Authors assumed that some depressive subtypes have a different autoimmune profile. In the study depressive episodes are treated with SSRIs and SNRIs but literature support the idea that SSRIs and SNRIs have a worse response on atypical depression. The non response of atypical depressions (50% vs 33%) might have an influence on the difference of outcome between autoimmune depressive subtypes. This is not statistically significant but the sample is not large enough to exclude a type B error.

Atypical patients are over-represented in the 'partial responders' group and this is of course in accord with the literature. The percentages are all in accord with the literature, when we consider naturalistic studies. We wish not to comment this issue, because it represents a triangular relationship. If the results were contrary, this would constitute a finding to comment on. A note on this was added in the discussion.

The discussion is verbose. The role of thyroid function in depression might be faced only in relation with the specific study hypothesis.

The discussion was re-written

Discretionary Revisions (which the author can choose to ignore)

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
Unable to decide on acceptance or rejection until the authors have responded to the What next?:
major compulsory revisions
An article whose findings are important to those with closely related research Level of interest:
interests
Needs some language corrections before being published Quality of written English:
Yes Statistical review:
Declaration of competing interests:
none

We are looking forward to receiving your response

Best regards

Dr KN Fountoulakis