Author's response to reviews

Title: Neurocognitive Function in children with Compensated Hypothyroidism: lack of short term effects on or off thyroxin

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Editors
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Re Ms: # 1764671955835834 - Comparative study of cognitive development in children with compensated hypothyroidism

Dear Editors:

We wish to thank the reviewers for their comments and suggestions which we have found helpful. We have addressed the issues as noted below and feel that the changes have focused the paper better and strengthened the manuscript.

Response to Reviewers:

Reviewer 1:

1. Introduction: "A sentence is needed to articulate the difference between "overt" and "compensated" hypothyroidism". The difference has been articulated in the introduction and the statement that those with compensated hypothyroidism generally have no clinical signs of hypothyroidism has been inserted.

"Last two sentences of the introduction are confusing:" The next to the last sentence in the Introduction has been revised to clearly state that the study evaluated the effect of thyroxin on cognitive function. The last sentence was confusing and has been struck.

2. Methods: "It would be helpful to state at the outset....." It is now stated that charts of all 21 subjects identified with compensated hypothyroidism were reviewed. Later in the results it is stated that 14 consented and 11 completed the study and were therefore evaluable.

3. Methods protocol: "There is a potential problem with obesity. Obese children can have mild elevations of TSH and normal T4 and it is important to state how or whether these were included or not." BMI of the children ranged from the 22 - 97 % for age with a mean of 64.5 %. This is now stated in the first paragraph of results. Thus, none were obese and all had BMIs which were within 2 SD from the mean for age.

4. "Methods protocol: what is the difference in terms of hypothyroid pathology and consequence on cognitive function, between children initially on thyroxin therapy who remain euthyroid 6-8 weeks after discontinuation, versus those who require resumption of therapy?" The further confusion appears on page 10, when it is stated that of the 5 subjects in group 2, 2 were placed back on treatment and 3 were not. Were these 3 therefore subjects now to be considered normal, with only past thyroid function tests possibly abnormal? The bottom line is that the presumed differentiation between the different clinical groups is...
difficult to maintain." The reviewer indeed has identified a confusing clinical area, but one which presents itself frequently to the clinician. There are patients who have mild elevations of TSH at one point in time but not at others, often for unidentifiable reasons. As the reviewer suggests, presumably the difference between the groups is that the 2 whose TSH concentrations were elevated off thyroxin and the 3 whose TSH was normal off thyroxin, is that the former had some subtle permanent thyroid dysfunction, while the latter group had transient and reversible thyroid dysfunction. We could not identify any difference in cognitive function between the 2 groups but the numbers are too small to say much.

5. "Discussion p. 15 This section begins by talking about ADHD. This has not come up so far. Nor has it been stated whether children with ADHD have a greater prevalence of thyroid disease or compensated hypothyroidism. Adding an introduction to this concept will help". The following paragraph has been added:

To date, the only clear association between thyroid dysfunction and ADHD is in children with thyroid hormone resistance (15). A recent study found no correlation between T4 concentrations on neonatal screening and the later development of ADHD (16). However, the study did not examine TSH concentration which is a more sensitive indicator of thyroid dysfunction, and therefore may have missed those with mild thyroid dysfunction. A study in rats has shown that transient thyroid depletion in the newborn period is associated with attention deficit like behavior later in life (17).

6. See response to # 4. above.

Discretionary Revisions:

1. "Sentence that begins with "Song it al showed......" is unclear "and the next sentence says...." For the purposes of this publication is really not needed, or, if desired, must be made more explicit and clear. The first sentence has been revised to clarify the meaning and the second sentence has been struck.

2. "for children with congenital disorders... the pattern of data seen here clearly..." "This seems to be overstated". This entire paragraph has been deleted.

3. "Conclusion is perhaps a bit overstated". The conclusion states "This study suggests that, despite the absence of behavioral manifestations of distractibility and hyperactivity, children with a history of compensated hypothyroidism may have significant deficits in attention on clinical measures (TOVA, TOH) relative to the normal distribution as defined". We believe the words "suggests" and "may have" are sufficiently tentative so as not to overstate. The main point of the paper is the last sentence of the conclusion.

Response to Reviewer # 2:

1. "Address the issue of absent control group": The main purpose of the study was to examine the effect of thyroxin therapy on neurocognitive function in children with compensated hypothyroidism. As such, each child served as his or her own control on and off thyroxin. This is now stated in the methods. For the group as a whole, the neuropsychological studies were compared to normative data derived from the general population. This is clearly delineated in the heading of the section reporting these results ("Cognitive function as compared to the normal distribution"). A secondary outcome of the study was that, as a group, the children appeared to a tendency towards attention deficit. This issue is clarified in methods and is reiterated in the results section where it is clearly stated that the scores were compared to those seen in a normal population of age matched children. The discussion section has been reorganized to emphasize the distinction between the controlled data (effect of thyroxin) and the comparisons to normative data. Finally, this issue is reemphasized in the final paragraph of "Discussion" delineating the limitations of the study.

1. Describe the differences between congenital and acquired hypothyroids children, and any relationship to age at diagnosis. The differences are summarized in Table II. and also stated in 1st paragraph of Results.

3. "Statistical differences should be easily identified in the tables": The data in Table III simply show the composite scores on visit 1 and 2 for those on and off thyroxin and combined for each visit. As stated clearly in the text, there were no statistically significant differences between those on and off thyroxin and
between visit 1 and 2 for the combined groups. Hence there are no statistical designations in the table. The only areas in which there were statistically significant differences between study subjects and the general population was in the Tower of Hanoi. This is clearly stated in the results section and is not represented in a table.

Minor changes:

"off of thyroid hormone" should be changed to "off thyroid hormone". The word processor search engine did not find any instances of "off of thyroid hormone" but did find two instance of "off of thyroxin" which was changed to "off thyroxin".

In addition, we have made the following changes in the paper:

The title has been changed to:

"Neurocognitive Function in children with Compensated Hypothyroidism: lack of short term effects on or off thyroxin" which better describes the outcomes of the study.

One author has married and her name has changed (Bracken)

We have added more details about the subjects in the methods section to clarify some of the confusion raised by the reviewers.

Reviewer # 2 raised the issue that due to the age range, not all children would have been expected to complete all tests. This is what we had meant by the sentence: "In some cases, scores of some subtests were not available due to missing data" in Statistics. This statement has now been expanded to: "Since the age range of children studied was considerable and not all children were able to perform all tests (e.g. Judgment of Line Orientation), some scores were not available."

The Teacher Report Form was not included in the Child Behavior Checklist because most of the children were studied in the summer months when school was out of session. This is stated in the methodology section.

We have added a section: "Behavioral Functioning" at the end of Results.

We have added the following statements in the discussion to relate our findings to the adult literature and animal literature and added references (12, 15, 16 & 17):

"As primary outcome measure, this study did not reveal an influence of thyroxin therapy on neurocognitive function in this small group of children with compensated hypothyroidism. Similar studies of the effect of thyroxin supplementation on neurocognitive function in adults with subclinical hypothyroidism have revealed variable results, but the largest study found no effect (studies summarized in ref. 12). The developing brain is known to be more sensitive to thyroxin deprivation than the adult brain, hence this remains an open question in children. Since this was a short term study, it is possible that a longer period of being on or off thyroxin therapy may have yielded different results. However, for safety considerations, it was considered important to carry out a short term study before examining the effects of thyroxin withdrawal and therapy over a longer period in this population.

and

"There is controversy concerning the relationship between thyroid dysfunction and ADHD. To date, the only clear association between thyroid dysfunction and ADHD is in children with thyroid hormone resistance (15). A recent study found no correlation between T4 concentrations on neonatal screening and the later development of ADHD (16). However, the study did not TSH concentration which is a more sensitive indicator of thyroid dysfunction, and therefore may have missed those with mild thyroid dysfunction. A study in rats has shown that transient thyroid depletion in the newborn period is associated with attention deficit like behavior later in life (17)."

Table I: "Animals" has been changed to "Controlled oral word association: animals" and "WCJ" has been changed to "WJII" for added clarity
We hope that you will find these changes acceptable and will publish our manuscript in BioMed Central.

Sincerely,

Thomas A. Wilson, MD
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