PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cognitive function in idiopathic intracranial hypertension — a prospective case-control study
AUTHORS	Yri, Hanne; Fagerlund, Birgitte; Forchhammer, Hysse; Jensen, Rigmor

VERSION 1 - REVIEW

REVIEWER	Michael Wall University of Iowa Departments of Neurology and Ophthalmology
REVIEW RETURNED	05-Dec-2013

GENERAL COMMENTS	This paper needs review by a neuropsychologist. I am not expert on the tests they performed and what they mean. This is a well done study except for the control group that ideally would be obese subjects with chronic daily headache. The authors report their experience testing cognition in IIH patients. The study protocol and statistical analysis are well thought out and appropriate except for the one issue with controls mentioned below. This is difficult research and much effort has been given to control many potential confounds. The introduction should include a review of previous studies of cognition in IIH. Some of the information about IIH in the introduction is not needed and can be deleted. The major problem with the study is the control group should be obese subjects with chronic daily headache (not an easy group to find). Most patients with IIH have chronic daily headache (14 in current series) so comparison to migraine patients with intermittent headache is problematic. This should be added to the discussion. The way to answer the main question posed would be to test controls with both obesity and chronic daily headache. Could the interaction of these two factors account for the findings? This should be discussed. The authors should compare the subjects with daily headache with those that do not have daily headache. Also, are there studies that give the effect of chronic pain on these measures? If so, could any of the findings be due to chronic pain? The authors conclude IIH subjects have moderate to severe cognitive deficits. I have managed hundreds of IIH patients over many years. They do not appear to have moderate to severe cognitive deficits (many hold down high levels jobs) and do not report changes in cognition in the moderate to severe range when asked. Why is there this dissociation? Could it be the changes are mild? It appears that the authors are suggesting the presence of ICP

	causes brain damage since testing can remain abnormal even when CSF pressure normalizes. If so, this damage must be minimal as brain volume is normal in IIH. This should be discussed.

REVIEWER	Michael Bjørn Russell Head and Neck Research Group Akershus University Hospital Lørenskog, Oslo Norway
REVIEW RETURNED	06-Jan-2014

GENERAL COMMENTS	Material and methods section state that people with medication use or comorbid disorder that could affect cognition were excluded. However, it would still be fine with a list of comorbidity of the patient population, since comorbidity is expected to be higher among those with IIH than controls, due to obesity. The control group is flawed by the lack of match for BMI. Furthermore, the advantage of a control group in this study is unclear, and probably explained why other rephrained for including a control group. The most important result in my opionion is improvement in the IIH group from baseline to follow-up. Here each person serves as it's own control. Still we are left with a black box, since cognitive function prior to IIH headache disorder is unknown. Table 1. Is it correct that all participants were men? Please add for how many years the patients experied IIH prior to diagnosis. This is an important aspect, since short duration of the IIH would indicate that it is not likely it had a major impact on cognition, while long duration might have that effect. Beside obesity, depression/dysphoric mood can also affects cognition. Obesity and frequenct headache are often associated with depression/dysphoric mood. A paragraph should be added to the results section, if these data are available. A paragraph on this aspects should be added to the discussion irrespectively. The mean ICP decreased, but the mean ICP was still 25.9 cm H2O, which is higher than normal ICP which is usually defined as < 20.0 cm H20. Could that be the reason for the lack of effect observed in the study. Did the people with ICP below 20.0 cm at follow-up improve more that those with ICP above 20.0 cm H20? Did large change vs. small change in ICP matter?

VERSION 1 – AUTHOR RESPONSE

To Mr. Michael Wall

Thank you for your very positive and constructive comments on our study. We appreciate your expert opinion and have now tried to revise our manuscript according to your comments suggestions. Please find below our repsons to your comments.

#The introduction should include a review of previous studies of cognition in IIH. Some of the information about IIH in the introduction is not needed and can be deleted#

1) The Introduction: Thank you for your comments on the introduction. The introduction has now been revised and a short review of previous studies on cognition in IIH has been added.

#The major problem with the study is the control group should be obese subjects with chronic daily headache (not an easy group to find). Most patients with IIH have chronic daily headache (14 in current series) so comparison to migraine patients with intermittent headache is problematic. This should be added to the discussion.#

2) Control group: Pain and obesity are definitely all factors that could be considered potential confounders in the assessment of cognitive function. However, the vide range of factors potentially affecting performance in cognitive tests and as mentioned the ideal match is very difficult to achieve. Although effort was given to control for as many confounders as possible, such as age, education, and gender, and including ongoing headache, we fully agree and acknowledge that ideally we should have included a control group of obese patients with headache. The challenges of achieving a good and solid control group, has now been added to the section discussing the limitations of the study (page 20).

#The way to answer the main question posed would be to test controls with both obesity and chronic daily headache. Could the interaction of these two factors account for the findings? This should be discussed. The authors should compare the subjects with daily headache with those that do not have daily headache. Also, are there studies that give the effect of chronic pain on these measures? If so, could any of the findings be due to chronic pain? #

3) BMI: BMI in our patients ranged from normal to morbidly obese (24.2 – 48.8 kg/m2). Analyses of cognitive performance performed within the patients group showed no significant effect of BMI on any single test in the battery (page 8 and 11).
4) Chronic pain: We appreciate your concern that chronic pain may account for some of our findings of cognitive impairment. Many studies have investigated pain-related cognitive impairment and there seems to be evidence to support the relationship between mild neuropsychological deficits in selected domains including many of the domains tested in our study (1,2). The effect of pain itself on cognitition is, however, rather unclear as chronic pain is commonly accompanied by opioid use and depression which makes the separation of causal threads very difficult. In one large study of patients with chronic arthritis it was demonstrated that the effect of pain on cognition disappeared when controlling for depression, suggesting that a pain-cognition relationship may be mediated by depression (3).
As recommended we compared the cognitive performance of patients with (n=10) and without (n=21) chronic headache. We found no significant effect of chronic headache on test performance. According to the comments from reviewer #2 we also compared performance of patients with (n=8) or without (n=23) co-existent depression and found no significant difference between the two groups (page 8 and 11). It thus seems less likely that chronic pain or depression account for our findings of impaired cognition. However, the question is still highly relevant and thus the potential impact of chronic headache, BMI and depression has been emphasized in the discussion (page 19-20).

#The authors conclude IIH subjects have moderate to severe cognitive deficits. I have managed hundreds of IIH patients over many years. They do not appear to have moderate to severe cognitive deficits (many hold down high levels jobs) and do not report changes in cognition in the moderate to severe range when asked. Why is there this dissociation? Could it be the changes are mild? #

5) Range of cognitive deficits: Cognitive function in our patients showed rather great variation from above mean performance of the healthy controls to substantially below. We thus completely agree that in some patients with IIH there seems to be no affection of cognitive function. However in the neurological setting of the Danish Headache Center we experience surprisingly poor compliance to treatment and follow-up in patients with IIH and as many patients complain of difficulties in complex daily activities and work situations we were prompted to examine the cognitive function in these patients. We acknowledge that deficits in the range found in our study may be clinically modest and have modified our statements of severity (page 17 and 20).

#It appears that the authors are suggesting the presence of ICP causes brain damage since testing can remain abnormal even when CSF pressure normalizes. If so, this damage must be minimal as brain volume is normal in IIH. This should be discussed. #

6) Structural damage to the brain: We agree that neuro-imaging has not yet identified structural damage to the brain in IIH and that such damage, if any may be subtle. We would have expected any structural alterations caused by raised intracranial pressure to have been reversible upon ICP normalization and were surprised that follow-up did not show improvement in test-performance. However, even with reversibility of structural changes, three months may not have been enough to restore a compromised neuronal function. This has now been further discussed in the manuscript (page 19).

To Mr. Michael Bjørn Russell

Thank you for your very constructive and helpful comments on our study. We appreciate your suggestions and have now tried to revise our manuscript according to your comments and suggestions. Please find below our response to your comments.

#Material and methods section state that people with medication use or comorbid disorder that could affect cognition were excluded. However, it would still be fine with a list of comorbidity of the patient population, since comorbidity is expected to be higher among those with IIH than controls, due to obesity. #

1. Co-morbidity: as suggested, we have included a list of co-morbid disorders in the patients to the result section (“Demographics and clinical characteristics”, page 9).

#The control group is flawed by the lack of match for BMI. #

2. BMI: We fully acknowledge that our control group would ideally have included obese individuals as

obesity and related co-morbidities could potentially affect cognitive performance. BMI in our patients ranged from normal to morbidly obese (24.2 – 48.8 kg/m2). Analyses of cognitive performance performed within the patients group showed no significant effect of BMI on any single test (page 8 and 11).
The possible confounding is still an important a relevant discussion and has been given attention in the discussion of study limitations (page 20).

Furthermore, the advantage of a control group in this study is unclear, and probably explained why other rephrained for including a control group. The most important result in my opionion is improvement in the IIH group from baseline to follow-up. Here each person serves as it's control. Still we are left with a black box, since cognitive function prior to IIH headache disorder is unknown.

3. Relevancy of a control-group: When examining neurocognitive functions it is necessary to have reference data from a healthy population to assess whether deficits are present. The main factors that influence cognition are age, education, and less so, gender, all factors that were taken into account when matching the healthy controls to the included patients. Using published normative data (as done by the other studies that you mention) is also an option, but we did not have normative data available for all the tests in Danish. In addition factors possibly influencing test performance such as headache, pre-morbid intelligence, education, sex, age and examiners skills would have been difficult to account for. We agree that the patient may ideally serve as its own control. However, as you mentioned we do not have access to pre-morbid test performance and as no overall significant improvement was found at follow-up these data did not provide evidence on their normal function. In addition comparison from baseline to follow-up is complicated by test-retest effect as briefly mentioned in the discussion (page 18).

#Table 1. Is it correct that all participants were men? #

4. Table 1: You are correct that all patients were women, not men. The mistake has now been corrected. Thank you for your alertness.

#Please add for how many years the patients experied IIH prior to diagnosis. This is an important aspect, since short duration of the IIH would indicate that it is not likely it had a major impact on cognition, while long duration might have that effect.#

5. Disease duration: We agree that cognitive dysfunction would be likely to depend on disease duration and that this information is highly relevant. We only included patients within a week of diagnosis, but duration of symptoms before diagnosis showed great variation. Onset may be difficult to define as symptoms are often insidious. However, the estimated time of symptom onset was specified in the standardized interview and is given in Table 1.

#Beside obesity, depression/dysphoric mood can also affects cognition. Obesity and frequenct headache are often associated with depression/dysphoric mood. A paragraph should be added to the results section, if these data are available. A paragraph on this aspects should be added to the discussion irrespectively.#

6. Effects of depression on cognitive function: You are very correct that depression, known to be associated with IIH has been shown to affect some areas of cognitive performance and patients were explicitly asked for previous or current depression in the standardized interview. Eight of 32 (29%) reported depression (now also listed in the section of "Demographics and clinical characteristics", page 9).
To test for obvious effects of depression on cognitive function we compared performance of patients with (n=8) and without (n=23) co-existent depression. We found that in our material depression was

not significant for test-performance. It thus seems less likely that depression accounts for our findings of impaired cognition. However, the question is still highly relevant and, as suggested in your comments, the potential impact of depression as along with chronic headache and BMI has been added to the discussion (page 20).

#The mean ICP decreased, but the mean ICP was still 25.9 cm H2O, which is higher than normal ICP which is usually defined as < 20.0 cm H20. Could that be the reason for the lack of effect observed in the study.
Did the people with ICP below 20.0 cm at follow-up improve more that those with ICP above 20.0 cm H20?
Did large change vs. small change in ICP matter? #

7. ICP and cognitive function: It is correct that normal ICP has been defined as below 20 cmH2O. However recent ICHD-3 beta and the revised Dandy criteria define intracranial hypertension as an ICP above 25 cmH2O (4,5). Using these definition 50% of our patients had normal ICP at follow-up. Lumbar puncture manometry has its limitations and as only 5(18%) patients had ICP ≤ 20 you may be correct that ICP might still have been elevated in more than half of the patients.
As recommended we compared patients with ICP opening pressure below and above 20 cmH2O at follow-up. We found no significant difference in cognitive improvement from baseline in the two groups. Neither was there any significant relationship between numerical change in ICP from baseline to follow-up and change in cognitive performance (page 8 and 14). The link between intracranial hypertension and cognitive dysfunction therefore remains unsolved.

Reference List

1. Block C, Cianfrini L. Neuropsychological and neuroanatomical sequelae of chronic non-malignant pain and opioid analgesia. NeuroRehabilitation 2013;33:343-366.
2. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. Prog Neurobiol 2011;93:385-404.
3. Brown SC, Glass JM, Park DC. The relationship of pain and depression to cognitive function in rheumatoid arthritis patients. Pain 2002;96:279-284.
4. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629-808.
5. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology 2013;81:1159-1165.

VERSION 2 – REVIEW

REVIEWER	Michael Wall University of Iowa, USA
REVIEW RETURNED	05-Feb-2014

GENERAL COMMENTS	"As recommended we compared the cognitive performance of patients with (n=10) and without (n=21) chronic headache. We found no significant effect of chronic headache on test performance. According to the comments from reviewer #2 we also compared performance of patients with (n=8) or without (n=23) co-existent depression and found no significant difference between the two groups (page 8 and 11)." As I am sure the authors know, failure to find a "significant" difference does not mean no difference exists. First, please give the magnitude of the all differences found with recent subgroup

	analyses and then comment on whether there was there adequate power to detect a clinically significant difference in these measures. With regard to point 6), there is no plausible evidence there is parenchymal brain damage in IIH patients. Brain edema reports have been adequately refuted by modern neuropathological techniques. There certainly is not intracellular edema or there would be mental status changes. It is best to say there is no plausible evidence for brain damage and that suggestion should be deleted. Maybe rewiring of brain networks but damage is unproven.

VERSION 2 – AUTHOR RESPONSE

Mr. Michael Wall

Thank your for your valuable suggestions to improve our manuscript. We have now revised our manuscript accordingly and we hope the improvements made will meet your expectations.

#As I am sure the authors know, failure to find a “significant” difference does not mean no difference exists. First, please give the magnitude of the all differences found with recent subgroup analyses and then comment on whether there was there adequate power to detect a clinically significant difference in these measures.#

Magnitudes and 95% confidential intervals of differences between patients with and without depression and patient with and without chronic headache and the effect of BMI are now provided for all the 19 individual test variables in Table 4 (supplementary online table).
Magnitudes and 95% confidential intervals of the overall test differences (mean outcome for all 19 tests) in patients with or without chronic headache and depression are given in the results section (page 11) along with estimates and 95% confidential limits for the effect of BMI.
The rather wide 95% confidential limits of the estimated effects of chronic headache and depression indicate that results should be interpreted with caution and we fully agree that our sample size study may not provide sufficient power to detect a true difference. Sufficient power to detects differences <1 SD would require more than the 31 included patients. However, inclusion of chronic headache, depression or BMI in to the mixed linear model of cognitive function had no effect on the other co-variables used in the model and thus there is no evidence of confounding by these factors within the patient group.
The limitations of sample size and the statistical uncertainty has now been commented further in the discussion (page 20)

#With regard to point 6), there is no plausible evidence there is parenchymal brain damage in IIH patients. Brain edema reports have been adequately refuted by modern neuropathological techniques. There certainly is not intracellular edema or there would be mental status changes. It is best to say there is no plausible evidence for brain damage and that suggestion should be deleted. Maybe rewiring of brain networks but damage is unproven.#

Thank you. According to your comments we have emphasized that there is no plausible evidence for brain damage in IIH and have deleted the suggestions of brain edema (page 19).

Editorial comments:
#We prefer titles that frame the research question rather than 'headlining' the results.#

Thank you. We have now changed the title of our manuscript accordingly.