Author’s response to reviews

Title: Improvement in cognitive impairment following the successful treatment of endogenous Cushing’s syndrome-a case report and literature review.

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Author’s response to reviews:

Dr Darren Byrne

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Editor, BMC Endocrine Disorders,

Dear Dr Byrne,

Re: “Improvement in cognitive impairment following the successful treatment of endogenous Cushing’s syndrome-a case report and literature review”

Thank you for giving us an opportunity to revise our manuscript titled “Improvement in cognitive impairment following the successful treatment of endogenous Cushing’s syndrome-a case report and literature review”. We would like to thank the Reviewers for providing us with the detailed overview of our manuscript and for their constructive comments which helped us to improve our manuscript.

We have revised our manuscript according to the Reviewers’ comments. We have provided a detailed response letter with all required changes being highlighted in yellow colour.
This work has not been previously published nor submitted for publication elsewhere, the authors declare no relevant conflict of interest, and consent to publication of the work in BMC Endocrine Disorders. All authors have approved this manuscript for its submission.

We feel that our manuscript contributes to the existing limited literature on the acute and long-term detrimental effects of hypercortisolaemia on brain function. As such; we believe that these findings would be of wide interest to the readers of BMC Endocrine Disorders.

Yours sincerely,

Dr Malgorzata Brzozowska
MD, FRACP, PhD.

Response to Reviewer 1 Comments

Comment 1

Abstract (page 1): It would be recommendable to mention the assessment tool used to evaluate neurocognitive function. · In the conclusions section of the abstract, authors emphasize the importance of early detection of Cushing's syndrome to prevent neuropsychiatric disorder, but not neurocognitive deficit. Are there any specific reasons for this?

Our reply

Thank you for pointing out this omission. The additional sentence has been added to the abstract “The patient’s progress was evaluated using serial clinical observations, functional assessments, Mini-Mental Status exams and through the formal neuropsychological report.” (case presentation of the abstract, lines 26 to 28) and “to prevent neurocognitive impairment and neuropsychiatric disorders” (conclusion part of the abstract, line 33).

Comment 2

Case report (page 3): · How do authors evaluate cognitive impairments like "inattentiveness followed by progressive memory impairments, psychomotor retardation and inappropriate behavior"? Do authors use neuropsychological tests? Or is it only subjective complaints? It is one of the examples, but I think that information should be included in the text. Outcomes and follow-up (page 5): · Data of the repeated measures of performance status using the Barthel
Index during the different points of the follow-up would be useful to make clear the progression of the improvement. The same is true of the Mini-Mental state examination.

In order to address reviewer’s comments and to improve our manuscript we have described patient’s symptomatology in more detail based on our patient’s medical records from her multiple hospital admissions. As patient’s cognition had improved dramatically after the surgical removal of her pituitary adenoma the patient initially kept declining the formal neurophysiological testing. Finally, due to our repeat requests, the patient has undergone recent neurophysiological (April 2019) assessment, the results of which have been added to the manuscript.

We have added the more detailed timeline patient’s clinical progress to the “Case presentation” part of the manuscript, (lines 66 to 85).

“A 59-year-old woman, previously independent in activities of daily living and self-employed in the family business, presented with a progressive, over the period of 10 years, decline in cognitive function manifested as increasing social withdrawal, inattentiveness followed by progressive memory impairment, inappropriate behaviour, urinary incontinence and problems with balance. Furthermore she had episodes of an emotional lability, alternating between depressive symptoms with psychomotor retardation and agitation with paranoid ideation, insomnia and confusion. Patient’s presentation was complicated by a spontaneous (8mm) subdural haematoma treated with craniotomy and evacuation in year 2014 as well as by a single seizure during the perioperative period with a subsequent pulmonary embolism requiring temporary use of anticoagulation. Despite surgical evacuation of her subdural haematoma, the patient’s cognitive status continued to deteriorate due to superimposed episodes of delirium requiring multiple, 2nd monthly hospitalisations. Comprehensive geriatric assessment performed in between hospitalisations confirmed an impairment of patient’s executive function with impaired reasoning and problem solving skills. Her standardised Mini-Mental state examination (MMSE), brief (5–10 minutes) mental status questionnaire assessing attention, orientation, memory, language and visuospatial copying, revealed a score of 24/30, suggestive of cognitive decline. Three months prior to the neurosurgery her executive function severely declined to the point of requiring fulltime assistance with all daily living activities including her personal care and the need for regular antipsychotics and antidepressants with haloperidol, mirtazapine and levetiracetam.”

As well as to the “Outcome and follow up”, (lines 153 to 164).

“The patient regained full functional independence with activities of daily living and furthermore, she was able to reassume her duties helping with the family business finances, an improvement reflected by increased postoperative Barthel Index scores to 18 out of maximum 20 points (year 2017). Her mood has improved and therefore she no longer required treatment with antidepressants. The recent (year 2018) MMSE examination, revealed a total score of 30/30. A
more comprehensive neuropsychological assessment, performed 3.5 years after the successful neurosurgery (April 2019), revealed deficits in multiple cognitive domains including executive function with difficulty planning and organising, short term memory impairment for visually presented material and deficit in language with poor performance on confrontational word naming ability. The overall assessment was consistent with a mild cognitive impairment in a 63 year old woman, which was related to her previous CD.”

The following paragraph, describing the limitations of this case report, has been added to the “Discussion” part of the manuscript, (lines 190 to 200).

“In the present case, due to the severity of patient’s illness, her initial and postoperative cognitive assessments included serial clinical observations, mental status questionnaires together with functional assessments of her activities of daily living. Notably, the MMSE scoring may significantly underestimate cognitive impairment in a large proportion of individuals including patients affected by a mood disorder (1, 2). As our patient’s cognitive dysfunction has remarkably improved during her first postoperative 6 months, the patient was reluctant to undergo early neuropsychological testing to examine more discrete aspects of her cognitive functioning. The results of her detailed neuropsychological tests, performed at four years after her CS treatment, although indicative of the residual functioning impairment and deficits in visuospatial short term memory, point to a significant recovery of her brain cognitive function and ongoing remission from her CD.”

Comment 3

It would be recommendable (if possible) to add the brain imaging before and after the treatment of Cushing’s syndrome to provide evidence of the structural brain changes.

Our reply

The reviewer is being referred to the initially submitted two manuscript figures (1 and 2):

Figure 1: Title: Preoperative MRI showing small pituitary microadenoma.

Legend: Coronal MRI views show altered signal intensity within adenohypophysis T2 weighted sequence (Panel A), a region of delayed enhancement on the dynamic sequences (Panel B).

Figure 2: Title: Resolution of small vessel ischemia following the pituitary adenoma resection. Legend: Imaging studies obtained before and after treatment. Axial and sagittal FLAIR MRI images show the progressive resolution of microvascular ischaemic changes in the brainstem and cerebral hemispheres over time. Baseline (Panels A and D), at 2 years (Panels B and C) and at 3 years after resection of pituitary adenoma (Panels C and F).
Comment 4

Discussion (Page 6-9): · The discussion about the potential influence of hyperandrogenism and hyperprolactinemia on cognitive function decline and mood disorders is mandatory in this particular case. There are several studies that show the impact of hyperprolactinemia and sexual hormones on mood. ·

Our reply

In response to Examiner’s suggestion the following paragraph has been added to the “Discussion” part of the manuscript, (lines 313 to 344).

“Interestingly, the limited studies have shown negative impact of raised prolactin on a range of neurocognitive domains encompassing memory and executive function, anxiety and depressive behaviour as well as in regulation of stress responses (3-7). Furthermore, recent study demonstrated that treatment of hyperprolactinemia with cabergoline resulted in a cognitive enhancement in patients with prolactin-secreting pituitary adenomas (8). Mechanisms responsible for the cognitive deficits in patients affected by hyperprolactinaemia have not been fully explored. The limited in vivo or ex vivo animal studies linked hyperprolactinemia with the modulation of non-spatial cognitive tasks (6). The recent cross-sectional clinical study of female patients with prolactinomas, examined with MRI scans, demonstrated decrease in grey matter volume (GMV) in the left hippocampus and prefrontal cortex. These observed structural brain abnormalities were linked to the deficits in verbal memory and executive function on neuropsychological testing (9).

The treatment of CS in our patient resulted in an improvement in patient’s hyperandrogenism with the marked reduction in testosterone and DHEAS levels. The androgens play numerous, important roles in neurocognitive function and mood stability with the powerful effects on executive functioning. Androgens act through binding to intracellular androgen receptor proteins, localised in the multiple brain regions, with the high concentrations in hypothalamic and limbic regions (10, 11). Interestingly, the studies examining the effects of testosterone on cognition have produced conflicting results. The testosterone has been shown to exert sex-specific effects with both positive and negative influences on cognitive performance. The Dehydroepiandrosterone (DHEA) and its sulfate bound form (DHEAS) have neuroprotective effects and antiglucocorticoid activity(12). The low androgen levels have been associated with reduced cognitive function, poorer general sense of well-being, impairment of sexual function and depressive symptoms in elderly age (13-15). Low androgen levels have been reported as a risk factor for development of Alzheimer disease in men (16) while for women, their free testosterone level was negatively associated with verbal fluency, semantic memory, and episodic memory(17). Importantly, testosterone therapy improved the physical and emotional well-being as well as sexual function of postmenopausal women (18-20). Conversely, in the group of postmenopausal women, higher testosterone concentration was associated with lower scores for
verbal and visual memory, processing and psychomotor speed, executive functions, complex attention and cognitive flexibility (21),”

Comment 5

The limitations of their conclusions about this particular case are missing. There are medical factors other than glucocorticoid excess (as a previous subdural haematoma or syphilis) that can influence some of the cognitive outcomes in this particular case.

Our reply

We have added the following sentence to the discussion part of the manuscript, (lines 190 to 200).

“In the present case, due to the severity of patient’s illness, her initial and postoperative cognitive assessments included serial clinical observations, mental status questionnaires together with functional assessments of her activities of daily living. Notably, the MMSE scoring may significantly underestimate cognitive impairment in a large proportion of individuals including patients affected by a mood disorder (1, 2). As our patient’s cognitive dysfunction has remarkably improved during her first postoperative 6 months, the patient was reluctant to undergo early neuropsychological testing to examine more discrete aspects of her cognitive functioning. The results of her detailed neuropsychological tests, performed at four years after her CS treatment, although indicative of the residual functioning impairment and deficits in visuospatial short term memory, point to a significant recovery of her brain cognitive function and ongoing remission from her CD.”

The surgical evacuation of patient’s subdural haematoma in year 2014 did not lead to general cognition improvement. We have further clarified our patient’s progress in the text of the manuscript, section “Case Presentation”, (lines 72 to 77).

“Patient’s presentation was complicated by a spontaneous (8mm) subdural haematoma treated with craniotomy and evacuation in year 2014 as well as by a single seizure during the perioperative period with a subsequent pulmonary embolism requiring temporary use of anticoagulation. Despite surgical evacuation of her subdural haematoma the patient’s cognitive status continued to deteriorate due to superimposed episodes of delirium requiring multiple, 2nd monthly hospitalisations.”

The patient’s syphilis serology was negative with no past history of syphilis exposure or treatment.
Response to Reviewer 2 Comments

Comment 1

This interesting paper/article deals with the topic of the effects of cortisol excess on brain function and the possibility of recovery after Cushing's syndrome remission. First authors described a clinical case of a female patient who had significant worsening of her health with severe cognitive deficit who was diagnosed of CD only after 10 years from the development of signs and symptoms of the hypercortisolism. This paper focused on the possibility to obtain significant improvement of cognitive function after CS remission. As authors stated, complete reversal of neurocognitive impairment can unfortunately be only partial in these patients, thus early diagnosis of endogenous hypercortisolism is crucial.

I would like only some clarifications on the case report:

* When post-surgical cortisol measurement was assessed?

Our reply

The following sentence has been added to the “Outcome and follow up” part of the manuscript, (lines 131 to 132).

“Her serum cortisol level, which was measured on the fourth postoperative day, has decreased to 108nmol/L.”

Comment 2

What was the glucocorticoid initial dose given to the patient after surgery and why was she treated with prednisolone instead of hydrocortisone?

Our reply

The following sentence has been added to the “Outcome and follow up” section of the Manuscript, (lines 133 to 136).

“The patient was commenced on the supraphysiological prednisolone dose of 10mg/day to reduce her postoperative glucocorticoid withdrawal syndrome. The choice of glucocorticoid replacement therapy was influenced by the patient’s preference for once-daily glucocorticoid dosing. The patient had an uneventful post-operative recovery with a weaning regime of prednisolone up to 12 months post neurosurgery.”
Comment 3
Did the authors evaluate any changes in amygdala and hippocampus volume in their patient?

Our reply
The changes in amygdala and hippocampus volume were not evaluated as the initial MRI of patient’s brain did not include high-resolution three-dimensional (3D) sequences.

Comment 4
I was wondering why this patient was treated with cabergoline after surgery, as she had only a slight elevation of prolactin levels in a single measurement; furthermore, she was taking haloperidol which is known to induce prolactin elevation. Can authors comment on that?

Our reply
In response to Reviewer’s comment the following statement has been added to the “Outcome and follow up” section of the manuscript, (lines 140 to 144).

“As the patient’s prolactin level remained raised on repeated measurements, despite gradual withdrawal of antipsychotic medications, the patient was commenced on cabergoline for a period of 6 months (0.25 mg a week) with a subsequent decline in serum prolactin from 758mU/L to 299mU/L (2016). Her prolactin levels remain within the reference range after cabergoline cessation.”

Additionally, we have also added the paragraph outlining the cognitive benefits associated with treatment of hyperprolactinemia to “Discussion” section of the manuscript, (lines 313 to 324).

“Interestingly, the limited studies have shown negative impact of raised prolactin on a range of neurocognitive domains encompassing memory and executive function, anxiety and depressive behaviour as well as in regulation of stress responses (3-7). Furthermore, recent study demonstrated that treatment of hyperprolactinemia with cabergoline resulted in a cognitive enhancement in patients with prolactin-secreting pituitary adenomas (8). Mechanisms responsible for the cognitive deficits in patients affected by hyperprolactinaemia have not been fully explored. The limited in vivo or ex vivo animal studies linked hyperprolactinemia with the modulation of non-spatial cognitive tasks (6). The recent cross-sectional clinical study of female patients with prolactinomas, examined with MRI scans, demonstrated decrease in grey matter volume (GMV) in the left hippocampus and prefrontal cortex. These observed structural brain abnormalities were linked to the deficits in verbal memory and executive function on neuropsychological testing (9).”
Comment 5

I think authors should discuss the impact of glucocorticoid receptor polymorphisms on cognitive function

Our reply

Thank you for your comment. The following paragraph has been added to the “Discussion” part of the manuscript, (lines 272 to 287).

“The metabolism of glucocorticoids is regulated by enzymes 11-beta-hydroxysteroid dehydrogenases (11b-HSDs)(22). Polymorphisms in the (GR) gene may contribute considerably to the diverse individual responses to the glucocorticoids(23). The variability in the expression of GR in pituitary and adrenocortical cells may alter the sensitivity of the hypothalamus-pituitary-adrenal (HPA) axis with subsequent differences in body composition and metabolic factors (23). The ER22/23EK polymorphism of GR gene has been associated with partial form of GC resistance (24) while BclI and N363S polymorphisms have been linked with higher GC sensitivity (25, 26). Notably, GR polymorphisms in BclI and N363S as well in 1β-HSD1 may increase individual predisposition to mood disorder including depression (27, 28). Interestingly, recent reports cautiously linked genetic variants of GR with the degree of postoperative neuropsychiatric disorders in CS patients. In a previous study the polymorphisms in 11β HSD type 1 and NR3C1 Bcl1 genes influenced the severity of cognitive impairments in processing and reading speed, auditory attention and working memory together with fatigue (29). The molecular mechanisms of these observations remain largely unexplained; therefore, much more must be learned about the HPA axis and its regulation.”

Comment 6

Minor point: * Once an abbreviation has been introduced, they should be used throughout the rest of the paper (i.e. CS for Cushing’ syndrome and CD for Cushing’s disease)

Our reply

The abbreviation has been corrected appropriately, thank you.

References


