Author’s response to reviews

Title: Predictive factors of adrenal insufficiency in patients admitted to acute medical wards: a case control study

Authors:

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Author's response to reviews: see over
Dear Editor,

Please find enclosed the revised version of the manuscript entitled “Predictive factors of adrenal insufficiency in patients admitted to acute medical wards: a case control study” by Jean-Baptiste Oboni and co-authors. The comments of the reviewers were helpful and this revised version has been ameliorated. We have addressed all points raised by the experts in the attached document and we hope that this has been done to yours and their satisfaction.

We confirm that this revised manuscript has not been published previously and is not under consideration for publication by another journal. All authors have approved this revised manuscript and agree with its submission to the BMC Endocrine Disorders.
I thank you for your consideration and hope the manuscript will be now acceptable to be published in the BMC Endocrine Disorders.

Sincerely,

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Answers to the reviewers' comments:

Reviewer #1 Philippe CHANSON:

1. “...It would be of great value to have a table indicating the precise diagnosis in the 32 patients....ACTH measurement would have been useful but is unfortunately unavailable”.

   Reply: accordingly, we included more data when available in the revised results section. Unfortunately the retrospective nature of the research does not allow having more precise details. This was included in the revised version of the manuscript: “For the 32 patients that had a confirmed adrenal failure, ACTH levels were available for 8 patients. On those 8 patients, 6 (18.7%) combined low levels of cortisol and elevated ACTH levels confirming the diagnostic of primary adrenal failure. The other 2 combined low levels of cortisol and ACTH, confirming a secondary adrenal failure. The final suspected diagnosis was secondary adrenal insufficiency for 26 patients (another 24 patients) (81.3%). Profound adrenal failure was identified for 14 patients (43.8 % of all cases) with cortisol levels < 100 nmol/l. We cannot rule out that several suspected cases of secondary adrenal insufficiency have been inadequately classified as secondary since the ACTH levels were missing. However, history of glucocorticoid withdrawal within weeks or months prior to the hospitalization was present in 13 patients (40.6 %), a clinical situation highly suggestive of secondary adrenal failure. All patients survived the acute event and were treated by stress doses of glucocorticoids. Six cases were excluded of the study considered as false positive since under glucocorticoid treatment during the ACTH-stimulation test. These patients had symptoms and/or signs that were potentially associated with adrenal insufficiency but none with adrenal crisis.”

2. “the other concern relates, on the contrary, to the potential presence of false negative tests, in particular if cases of partial corticotropic deficiency have been tested. At least this needs to be introduced in the Discussion as a limitation of the study”.

   Reply: accordingly, we included the following text in the discussion section: “We cannot rule out that partial adrenal failure may have been missed in the controls. The high dose ACTH test may identify only profound adrenal failure but not partial and subtle corticotropic failure that could have been detected by a low-dose (1 μg) ACTH stimulation challenge.”
Reviewer #2 Albertus BEISHUIZEN:

1. “The clinical judgement which led to ACTH testing has not been defined, what (objective) criteria were used?“

Reply: the retrospective nature of the study does not allow to precisely defining the clinical criteria used by clinicians to order the ACTH-stimulation tests. Based upon the constructive suggestion of the reviewer, we included a sentence in the methods section that describes the reasons which were usually used by clinicians to suspect an adrenal failure. “Unexplained signs such as hypotension, hyperkalemia, metabolic acidosis or hyponatremia were the key signs used by clinicians to order the ACTH-stimulation test in most clinical situations.”

2. “The cut-off used for AI diagnosis is controversial, why < 550 used and not looked upon various cut-off in their analysis? eg increment of < 100 or < 250?“

Reply: Dr Beishuizen is correct and we used the cut-off of 550 nmol/l since this assay is the one standardized in our Institution. The choice of this cut off value is based upon a publication by Wolfgang Oelkers (NEJM 1996; 335:1206-121) stating that a lower cut off of 550 nmol/L (20 mg/dL) is preferable to a cut off of 500 nmol/L (18 μg/dL), according to May et al (May ME, Vaughn ED, Carey RM. Adrenocortical insufficiency — clinical aspects. In: Vaughan ED Jr, Carey RM, eds. Adrenal disorders. New York: Thieme Medical, 1989:171-89). However, we tested the hypothesis with a lower cut-off sometimes described in the literature. A posttest cortisol response of less of 500 nmol/l has also been described as potential adrenal failure [ref 13]. In our case, lowering the cut-off to 500 nmol/l did not identify new cases in the defined control group. The choice of a higher cut-off value for passing the corticotrophin test could reduce the risk of overlooking secondary disease. A poor increment (< 248 nmol/l) has been described to be associated with adrenal failure in critically ill patients (Rothwell PM, Udwadia ZF, Lawler PG Cortisol response to corticotrophin and survival in septic shock. Lancet 1991; 337:582-83). This was not the case in our selected population admitted in a general internal medicine ward. However, we also described in this revised version of the manuscript, the number of potential adrenal insufficiencies detected based upon a reduced increment of the cortisol levels during the ACTH-test.
3. “How was treatment guided? Only GCs when the test was abnormal? Does a normal test exclude (R)AI in sick patients? In other word, were patients with a normal test never treated?”

Reply: accordingly, we included a better description of study and the following text was added in the revised version of the manuscript: “If adrenal failure was suspected, the ACTH-test was performed and in most cases, stress doses of glucocorticoid administrated for 48 hours. If the short ACTH stimulation test was normal, the glucocorticoid treatment was immediately stopped. In the proven 32 cases of adrenal failure, stress doses of hydrocortisone or prednisone were administrated and tapered. All patients with adrenal insufficiency left the hospital under glucocorticoid treatment.”

4. “In what time-frame were test result available to the clinician?”

Reply: as mentioned in point 3 and this is now clearly stated in the revised version, the test results were available with 48 hours after administration.

5. “Minor: the pro’s and con’s of ACTH testing should be discussed in larger extent. Were there any data on outcome?”

Reply: accordingly, we included a new text in the revised version. “The administration of supraphysiologic doses of ACTH (250 µg) is the standard challenge to test the adrenal responsiveness. This test has been widely used and several studies have reported an excellent agreement between peak cortisol concentrations obtained during the test and in the gold standard insulin tolerance test (Cunningham SK, Moore A, McKenna TJ. Normal cortisol response to corticotrophin in patients with secondary adrenal failure. Arch Intern Med 1983; 143:2276-79. Oelkers W. The role of high- and low-dose corticotrophin tests in the diagnosis of secondary adrenal insufficiency. Europ J Endocrinol 1998; 139: 567-70). The low-dose (1 µg) ACTH test has been proposed as a more sensitive test to detect secondary adrenal failure. When compared to the usual high dose ACTH test, the 1 µg stimulation test has demonstrated a slightly improved sensitivity. However, the handling of the commercially available ampoule of 250 mg of ACTH makes the test more difficult to perform. Furthermore, it has been suggested that the low dose ACTH may bind to the surface of the injection devices and may blunt the anticipated response (Murphy RJ, Livesey J, Espiner EA, Donald RA. The low dose ACTH test: a further word of caution. J Clin Endocrinol Metabo 1998; 83: 1558-13).”
6. “Minor: please provide data on ACTH tests results, in particular rise upon ACTH? Were there any patients with absolute AI, eg baseline < 100?”

Reply: As mentioned in reply number one of the first reviewer, we included in the results section, more data when available. Unfortunately the retrospective nature of the research does not allow having more precise details. We added the following text in the manuscript: “For the 32 patients that had a confirmed adrenal failure, ACTH levels were available for 8 patients. On those 8 patients, 6 (18.7%) combined low levels of cortisol and elevated ACTH levels confirming the diagnostic of primary adrenal failure. The other 2 combined low levels of cortisol and ACTH, confirming a secondary adrenal failure. The final suspected diagnosis was secondary adrenal insufficiency for 26 patients (another 24 patients) (81.3%). Profound adrenal failure was identified for 14 patients (43.8 % of all cases) with cortisol levels < 100 nmol/l. We cannot rule out that several suspected cases of secondary adrenal insufficiency have been inadequately classified as secondary since the ACTH levels were missing. However, history of glucocorticoid withdrawal within weeks or months prior to the hospitalization was present in 13 patients (40.6 %), a clinical situation highly suggestive of secondary adrenal failure. All patients survived the acute event and were treated by stress doses of glucocorticoids. Six cases were excluded of the study considered as false positive since under glucocorticoid treatment during the ACTH-stimulation test. These patients had symptoms and/or signs that were potentially associated with adrenal insufficiency but none with adrenal crisis.”
Reviewer #3 Bertil EKMAN:

1. “Introduction: adrenal insufficiency has to be defined more: primary, secondary, iatrogen etc..”

Reply: accordingly, we included the following text in the introduction section: “Adrenal insufficiency is defined as primary or secondary. Autoimmune and tuberculous adenitis are the principal etiologies for primary adrenal failure, which is characterized by low cortisol levels and elevated plasma concentrations of ACTH. Impairment of the hypothalamic-pituitary corticotropic axis is responsible for secondary causes of adrenal insufficiency. These situations are characterized by low circulating levels of cortisol and ACTH. The most frequent cause of secondary adrenal insufficiency is a tumour of the hypothalamic-pituitary region but administration of supraphysiologic doses of glucocorticoids may alter a normal hypothalamic response with secondary adrenal failure once individuals are weaned from the glucocorticoid treatment. Bilateral adrenalectomy or drug-induced adrenal insufficiency may be considered as iatrogenic etiologies for adrenal failure.”

2. “The second sentence is not easy to understand and come back in the end of the second paragraph”

Reply: accordingly, we modified the sentence. “Symptoms, signs and biological markers associated with adrenal failure are well known by clinicians [3, 4]. However the relative importance of these symptoms, signs and markers has not been fully studied in patients admitted in acute medical wards.”


Reply: accordingly, we modified the description: “Symptoms commonly associated with adrenal insufficiency are “fatigue” (lack of energy or stamina), abdominal pain, nausea, and dizziness (hypotension symptoms). The patient history may include a key element related to previous glucocorticoid treatment, thus increasing the risk of secondary adrenal failure related to glucocorticoid withdrawal.”

4. Why are basal cortisol levels inaccurate to assess adrenal function? Reference from 1953? No other literature? Combined ACTH and cortisol measurements in plasma for primary adrenal insufficiency are often diagnostic”
Reply: Dr Ekman is correct but the specific design of the study was to assess the prevalence of adrenal failure based upon the high-dose ACTH test. The latter is often required to definitively rule out a suspected adrenal insufficiency. The ACTH test is also often done in acute settings since plasma cortisol and ACTH levels may not be done uniformly in early morning. However, we included in the results section of the revised manuscript the prevalence of low basal levels of cortisol. “The prevalence of patients with basal cortisol < 165 nmol/l was of 8.9% (25/281 patients). In the 32 individuals with blunted response to the high-dose ACTH stimulation, the prevalence of low basal cortisol was of 59.4% (19/32 patients). In secondary adrenal insufficiency, the morning cortisol value < 100 nmol/l may indicates adrenal failure. If this criteria was used in our study, the prevalence of secondary adrenal failure diagnosed was of 5.0% (14/281 patients) for the entire cohort and of 43.8% (14/32 patients) for the proven patients with adrenal failure on ACTH-stimulation test.” Unfortunately the retrospective nature of the research does not allow having more precise details.

5. “Discuss more about the cut of levels for cortisol levels on basal conditions and in critical ill situation or like the population described in this paper, probably a large proportion with pneumonia or other bacterial infections. Is a cut off 550 nmol/l in cortisol after 250 µg Synacthen appropriate in the acute setting?”

Reply: accordingly, we introduced the following text in the discussion section: “Slightly over one out of ten (11.4%) patients with suspected adrenal insufficient admitted in an acute medical ward had an abnormal response to high-dose ACTH stimulation test defined as a 550 nmol/l cut-off for cortisol. A low baseline cortisol (< 165 nmol/l) not responding to ACTH is sometimes a recognized criteria to establish adrenal insufficiency. Partial secondary adrenal insufficiency might be present in critically ill patients, characterized by a poor cortisol response to ACTH despite normal baseline cortisol. A low cortisol increment (< 248 nmol/l) was measured in 19.2% (54/281 patients) of the entire cohort and in 68.8% (22/32 patients) of the individuals with proven adrenal failure. We cannot rule out that some patients with low cortisol increment to the ACTH challenge may have some functional adrenal insufficiency. However, this was probably not the case in our selected population hospitalized in a general internal medicine ward. All critically ill patients were excluded from the study since these patients are directly admitted in the intensive care unit of our institution.”
6. “**what is the difference of 1 µg and 250 µg? Is it important for this study?**

Reply: accordingly, we included a new text in the revised version which has been mentioned in the reply 5 of the Reviewer 2. “The administration of supraphysiologic doses of ACTH (250 µg) is the standard challenge to test the adrenal responsiveness. This test has been widely used and several studies have reported an excellent agreement between peak cortisol concentrations obtained during the test and in the gold standard insulin tolerance test (Cunningham SK, Moore A, McKenna TJ. Normal cortisol response to corticotrophin in patients with secondary adrenal failure. Arch Intern Med 1983; 143:2276-79. Oelkers W. The role of high- and low-dose corticotrophin tests in the diagnosis of secondary adrenal insufficiency. Europ J Endocrinol 1998; 139: 567-70). The low-dose (1 µg) ACTH test has been proposed as a more sensitive test to detect secondary adrenal failure. When compared to the usual high dose ACTH test, the 1 µg stimulation test has demonstrated a slightly improved sensitivity. However, the handling of the commercially available ampoule of 250 µg of ACTH makes the test more difficult to perform. Furthermore, it has been suggested that the low dose ACTH may bind to the surface of the injection devices and may blunt the anticipated response (Murphy RJ, Livesey J, Espiner EA, Donald RA. The low dose ACTH test: a further word of caution. J Clin Endocrinol Metabo 1998; 83: 1558-13).”

7. “**In the study by Patel et al...calculation of the increment is of no value.**

Reply: Dr Ekman is correct and our phrasing was inadequate. We modified the text: “Patel and co-authors described expected values of basal serum cortisol (> 250 nmol/l) and peak cortisol (> 600 nmol/l) after 250 µg intramuscular tetracosactrin in acute hospital admissions. However, the optimal cut-off for peak cortisol levels avec ACTH challenge has been questioned by several authors and current recommendations seem to include a minimum of > 18-20 µg/dl (> 500-550 nmol/l) to consider the ACTH response as adequate. These normal values vary dependent on laboratory and assay. In our department, the 550 nmol/l cut-off is considered as a normal response to the ACTH challenge. The minimum increment in serum cortisol is considered by Patel [14] and others as invalid to diagnose adrenal failure, because individuals who have a high basal concentration, due to normal circadian rhytmicity or acute stress, may be unable to increase further cortisol secretion.”

8. “**In all 6 are under glucocorticoid and excluded. How many of these had an adrenal crisis or sign of adrenal insufficiency? Nothing is said about the follow up of the 32 patients with abnormal response...?**

Reply: In all, 6 were under glucocorticoid and excluded. How many of these had an adrenal crisis or sign of adrenal insufficiency? Nothing is said about the follow up of the 32 patients with abnormal response...?”
Reply: Accordingly and as requested by reviewer 1 and 2, we have tried to give as many details as available in the context of the retrospective study. This new text was included: “For the 32 patients that had a confirmed adrenal failure, ACTH levels were available for 8 patients. On those 8 patients, 6 (18.7%) combined low levels of cortisol and elevated ACTH levels confirming the diagnostic of primary adrenal failure. The other 2 combined low levels of cortisol and ACTH, confirming a secondary adrenal failure. The final suspected diagnosis was secondary adrenal insufficiency for 26 patients (another 24 patients) (81.3%). Profound adrenal failure was identified for 14 patients (43.8 % of all cases) with cortisol levels < 100 nmol/l. We cannot rule out that several suspected cases of secondary adrenal insufficiency have been inadequately classified as secondary since the ACTH levels were missing. However, history of glucocorticoid withdrawal within weeks or months prior to the hospitalization was present in 13 patients (40.6 %), a clinical situation highly suggestive of secondary adrenal failure. All patients survived the acute event and were treated by stress doses of glucocorticoids. Six cases were excluded of the study considered as false positive since under glucocorticoid treatment during the ACTH-stimulation test. These patients had symptoms and/or signs that were potentially associated with adrenal insufficiency but none with adrenal crisis."

9. The first paragraph is a combined introduction/methods and result section and could be omitted

Reply: this was removed in the revised version of the manuscript

10. “low blood pressure is not a useful sign to discriminate adrenal insufficiency from other diseases. Still, according to the literature, this is a typical sign of acute AI. Do the authors really mean that low BP is not associated with AI because it did not discriminate against other serious diseases?”

Reply: We may have not been clear in the phrasing and modified the text as following: “Low blood pressure was present in half of patients in both cases with adrenal insufficiency and controls. This sign was – IN THE DESIGN OF OUR STUDY – not very useful to discriminate between patients with or without adrenal insufficiency. Low blood pressure remains a well recognized typical sign of acute adrenal insufficiency but clinicians should of course rule out many other clinical diagnosis responsible for low blood pressure [1, 4].”

11. “The control group is not healthy and probably even more ill than the adrenal insufficient patients so the only hint the clinician got is to ask the patient if they have used
glucocorticoids... the part about logistic regression is sophisticated but in this case a systematically description of the 32 cases should have give much more valuable information “

Reply: accordingly, the description of the 32 cases has been done (see point 8) in the limitation of the retrospective study. Dr Elman is correct by mentioning that the control group is not healthy and possibly more ill than the adrenal insufficient patients. However, this was the design of the study to try to identify, in a retrospective way, the key symptoms, signs or biological markers which may increase the likelihood to a have an altered ACTH-stimulation test. By using different model, we have demonstrated that the history of previous glucocorticoid treatment is the most significant key element that could help clinician to anticipate a potential adrenal insufficiency.