Author's response to reviews

Title: Pituitary apoplexy following shoulder arthroplasty -a case report

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

Ref: Pituitary apoplexy following shoulder arthroplasty – a case report

Thank you very much for considering the above paper for publication in your journal. The idea of presenting this case report was to highlight the fact that postoperative hyponatremia is routinely managed on conventional lines and a central cause for hyponatremia is least suspected, particularly of pituitary origin. The patient in our case report has been managed at a tertiary referral centre for his endocrine problems and there have been difficulties in tracking his medical reports and opinions from various medical specialists. As a result we have not been able to clarify on all the issues raised. However we have taken the suggestions from the reviewers on board and addressed the specific issues raised to a large extent. Accordingly the paper has been revised and we enclose the revised version for your consideration. A summary of the revision based on reviewers’ recommendation follows.

Under the heading Discussion the following are my comments:

1. No results of any blood tests are shown. Could they present blood levels in IS
(haemoglobin in mmol/l instead of gr %)? Could the authors present all principal plasma levels of hormones and electrolytes in the follow up? Do they have results from urine collections (volume, sodium level, osmotic density)? Could they show pituitary imaging?

The preoperative and postoperative blood results and the available hormone levels have been included. All lab values and the units mentioned are as per the hospital practice in the NHS. Urine analysis for osmolality has not been performed and we therefore are unable to provide these details.

2. Could they describe more in detail their actions concerning thrombotic prevention? For instance, was there presence of thrombophilia (strong positive family history)? The indication for acetylsalicylic acid in prevention of venous thrombosis sounds not straight for me (according to current guidelines). Do they have APTT levels or antiXa levels during LMWH therapy? Could they offer us the dosage used? Was there any co-morbidity conflicting with LMWH therapy (such as kidney function, other medication)? Could they estimate preoperative risk for a new venous thrombotic event in this case (using a score)? Did they restart any anticoagulation therapy after leaving the hospital?

The patient had a strong family history of DVT and PE and was on aspirin prophylaxis for cardio protection on the advice of his general practitioner. There were no other co-morbid factors apart from hypertension which was well controlled. The patient was prescribed LMWH prophylaxis (clexane 40 mg s/c once daily) in the immediate post-operative period after due consultation with the anaesthetist and the haematologist in the background of the above information. The issue of thromboprophylaxis in shoulder arthroplasty has not been well established due to the lack evidence and well controlled studies. The clinician therefore has to decide on clinical grounds only. LMWH prophylaxis does not require routine haematological monitoring for coagulation factors and therefore values of APTT, antiXa values were not assayed. Anticoagulation prophylaxis was discontinued after the first 48 hrs post op.

3. Could the authors comment more on the third cranial nerve defect, but also on the visual defects? Do they consider this as a primary or a secondary effect of pituitary damage? No lateral extension of the pituitary tumour had been described and this makes local pressure induced damage less likely to me. Or should these ophthalmologic defects be understood as a consequence of
absolute deficits in adrenal and thyroid hormones? Metabolic disturbances in the ocular muscles and/or retina layer? Mono-neuritis syndrome?

Cranial nerve involvement in pituitary tumour and apoplexy has been well described. Compression of the oculomotor nerve in its intracavernous course as the gland swells and impinges on the cavernous sinus, can give rise to mydriasis, limitation of eye movement and ptosis in that sequence. The superficially located pupillomotor fibres are easily prone to compression from space-occupying lesions, while microvascular disease affecting the vasa nervosum in the main nerve trunk usually spares the pupillary fibres. Pupillary involvement therefore forms an important clue in differentiating medical and surgical causes, although pupillary sparing does not always exclude a compressive lesion. Pituitary apoplexy can cause a sudden increase in the size of a pre-existing pituitary tumour and temporary impingement on the optic chiasm superiorly, although the tumour itself did not show any suprasellar extension on a later MRI, could have resulted in bitemporal hemianopia.

4. Could the authors comment more on the clinical approach of a pituitary insufficiency in the post-operative setting?
   +After their diagnosis they started hydrocortisone therapy orally. Why did they not give intravenous hydrocortisone in the early phase of treatment. Moreover, the dosage they propose is rather limited. Special reconsiderations for this restricted steroid stress dose? Do they have special recommendations with regard to daily dose steroid substitution in the background of a (strong) positive family history of venous thrombosis- Could the authors explain that there is a preferred sequence in starting corticosteroid hormone first with thyroid hormone afterwards? Could they discuss more in detail physiology behind hyponatremia in the presence of both hypothyroidism and hypocortisolism?- Why do they start testosterone substitution in a 62 years old men and why they choose the intramuscular route? What do they consider appropriate as the target level for testosterone at this age?

The patient was admitted to the acute medical unit and was reviewed by the endocrinologist for the above problem. Later for definitive care he was transferred to a tertiary referral centre and subsequently managed with hormone replacement therapy as deemed appropriate. We therefore are unable to comment on the treatment pathways, the choice and the sequence of treatment.
5) Was there, in retrospect, already some indication for the preoperative presence of pituitary adenoma in this patient (signs of hypogonadism, reduction in physical fitness, obstipation, depression, weight changes et cetera)?

No. There were no signs of pituitary dysfunction in the patient pre-operatively.

6) The description of the pituitary on MRI is not sound. Could they offer us some more information on: volume pituitary, suprasellar extension, pituitary stalk, infundibulum and its environment, ventricle space/indication for obstruction, location and anatomy of the internal carotid artery (aneurysm indeed present?). Did they consider retesting pituitary function six months after surgery? Should they extend their endocrine evaluation with testing for (partial) diabetes insipidus or a growth hormone deficiency?

On the MRI coronal views, the pituitary stalk was marked deviation of the pituitary stalk and the features were suggestive of adenoma. There was no extension of pituitary into the suprasellar cistern and the chiasm was not compressed. There was no abnormal anatomy of the internal carotid artery.

The pituitary functions were retested in the follow-up and the lab values are provided in the table. The decision to investigate and manage diabetes insipidus and growth hormone deficiency was entirely up to the physician and we are unable to comment on this further.

7) Was the aspirin discontinued before surgery? How long before surgery?

Aspirin was discontinued a week before the operation.

8) Please, provide all sodium values.- What was the hemoglobin value before surgery?

Provided as per the table.

9) It would be very attractive if the authors could show the CT scan which revealed a 15 mm low attenuation signal in the pituitary fossa as well as the MRI showing the macroadenoma.

CT scan images enclosed. Unfortunately MRI pictures cannot be provided as these have been performed in a different institution which we are unable to get hold of.

10) Please, depict the cortisol levels before and after synacthen stimulation as well as free T4 levels. Why was synacthen test performed instead of insulin tolerance
test?

Synacthen test reports are as per the table. We are unable to comment on the preference of synacthen test over insulin tolerance test as this is a decision of the treating physician.

11) Here, it is important to stress out that whether the central adrenal insufficiency is recent (secondary to apoplexy), there will be an adequate serum cortisol response to ACTH.

Thanks. This has been included in the manuscript.

12) The rest of pituitary function evaluation is not clear. Please, provide PRL, IGF-I, LH and testosterone levels as well.

Values are as per the table.

13) References; the references should be standardized

Thanks. Suggestions taken on board.