Peer Review File

Article Information: http://dx.doi.org/10.21037/gs-20-517.

Review comments

This manuscript shared a case of pituitary apoplexy, which was first considered as ruptured posterior communicating artery aneurysm. The provided information is useful for both the diagnosis and therapy, making it potentially publishable at Gland Surgery. However, here are some concerns.

1. Title: as Gland Surgery focuses on surgery, it's suggested to add vital information in the title. For example, useful information regarding the different manifestations and therapies.
Besides, add 'case report' in the title too.

Reply:

Thanks for your advice. We have revised the title to "**S**urgical treatment of a 72-year-old patient with headache, hyponatremia and oculomotor nerve palsy: a case report and literature review."

Changes in the text: we have modified our title as seen in title page.

2. Abstract: it's too short. Please provide more detailed information.
E.g. detailed medication, the clinical manifestation of this patient, the outcome and prognosis.
Importantly, what's unique of this case? (it's different from being rare) What NEW information does this manuscript add to our knowledge? Which part do authors focus on, the misdiagnosis or the therapy?

Reply:

Thanks for your valuable advice. We agree with your opinion.

Based on your valuable suggestions, we have revised relevant content in the Abstract section, as follows: *We report a case of a 72-year-old man with severe headache, nausea, vomiting, confusion and left oculomotor nerve palsy, who was initially considered as posterior communicating artery aneurysm (PCOAA) based on the presenting symptoms. Initial biochemical evaluation showed severe hyponatremia, hormonal evaluation identified multiple pituitary hormone deficiency and enhanced magnetic resonance imaging showed a large pituitary adenoma with signs of hemorrhage. A diagnosis of pituitary apoplexy and secondary hypopituitarism was finally made. The patient was treated with intravenous hydrocortisone 100 mg twice daily and oral levothyroxine 100 mg once daily. Appropriate venous transfusion with sodium was also used concomitantly to correct hyponatremia. After seven days of treatment, the patient's serum electrolytes normalized and he gradually recovered alertness. Then, the patient underwent transsphenoidal surgery for tumor removal. Left ptosis and oculomotor nerve palsy completely recovered three months after surgery. Postoperatively, hormone replacement therapy was essential for the patient with 20 mg hydrocortisone and 50 mg levothyroxine once daily. During the last follow up four years later, the patient was still on hormonal replacement and in good condition. So, for patients with pituitary apoplexy, we have shown that a semi-elective surgery after conservative treatment when the patient becomes clinically stable and hypopituitarism has been corrected is a good approach.*

(see page 2 *line 24-43 in the revised manuscript*)

Uniqueness of the case and new information:

In most cases, patients are treated either conservatively or surgically, but in our case, we performed a semi-elective surgery after seven days of conservative treatment when the patient was clinically stable and hypopituitarism had been corrected. The outcome turns out to be satisfactory and the prognosis is good. Therefore, we have shown through our experience that ocular paresis because of involvement of oculomotor cranial nerve in the cavernous sinus in the absence of visual field defects or reduced visual acuity is not in itself an indication for emergent surgery.

But surgery may be necessary even for conservatively treated patients later on, because rebleeding can also occur after conservative treatment.

Some may ask what is the point of conservative treatment during the acute phase of pituitary apoplexy if surgery will ultimately be necessary? Because patients with unstable condition and pituitary dysfunction are at increased risk perioperatively and may not carry a good prognosis. Moreover, in this emergent setting, the surgery may be performed by an on-call neurosurgeon rather than by a skilled pituitary neurosurgeon, which increases the risk of adverse events as well. Therefore, we recommend that the surgery be taken when the patient becomes clinically stable, unless the clinical situation warrants immediate intervention.

In the manuscript, we mainly focus on the treatment part, but the diagnosis part is also an important section which should be taken into consideration

Also seen in page 7,8 *line 179-218 in the revised manuscript*

3. Introduction: still, too superficial. Please provide an evidence-based introduction to show WHY/HOW this manuscript is different from previous ones.

Reply:

Thanks for your valuable comment. Based on your valuable suggestions, we have revised relevant content in the introduction section, as follows: *In more than 80% of patients, apoplexy is the first presentation of the underlying pituitary tumor; symptoms vary and often overlap with other common diseases. Therefore, the diagnosis of pituitary apoplexy is challenging and its appropriate management still remains a matter of debate as no large-scale, randomized controlled studies comparing conservative with surgical management for pituitary apoplexy are available. Whether conservative treatment or surgical intervention is the most appropriate management remains a matter of debate. Five large retrospective studies comparing the outcomes of surgically and conservatively treated patients with pituitary apoplexy have shown that conservatively treated patients had higher rates of recovery from oculomotor palsies and visual deficits. Yet a recent systematic review shows the opposite result and it suggests surgical intervention for patients with visual defects and ocular palsy.*

The optimal timing for surgery is a question as well if it is to be taken. Visual deficits used to be a neurosurgical emergency, but no difference in visual outcome is observed when surgery is performed within the first 3 days or during 4-7 days after the apoplectic event, whereas delays beyond one week may retard the return of visual function. Here, we present a case who underwent transsphenoidal surgery seven days after the pituitary apoplexy onset when he became clinically stable after conservative treatment.

(see page 3 *line 56-74 in the revised manuscript*)

4. Discussion: use one paragraph to list both tricks and pitfalls.

Reply: Thanks for your valuable comment. Based on your valuable suggestions, we have revised relevant content in the discussion section, as follows:

The presenting case is challenging both diagnostically and therapeutically. For the diagnosis part, if the patient does not have a known history of pituitary tumor, MRA and MRI will be necessary for differentiation of vascular and pituitary diseases. Digital subtraction angiography may not be the first choice in the emergency department as it is expensive and invasive, and complications may occur. For the treatment part, steroid replacement should be initiated as soon as the diagnosis is made. When patients' general condition improves after the replacement therapy, semi-elective transsphenoidal surgery is performed for tumor decompression. We do not recommend emergent surgery in patients who have remarkable adrenal insufficiency until the patient's hypopituitarism is corrected and general condition is stable. Because patients with unstable condition and pituitary dysfunction are at increased risk perioperatively and may not carry a good prognosis (12). Moreover, in this emergent setting, the surgery may be performed by the on-call neurosurgical team rather than by an experienced pituitary surgeon, which increases the risk of adverse events as well. Emergent neurosurgical decompression is necessary only when the patient has significant and deteriorating neuro-ophthalmic signs or declining level of consciousness in spite of the steroid replacement (20). In a word, early diagnosis and treatment of pituitary apoplexy are crucial for avoiding complications and preventing permanent visual defects

(see page 8 *line 201-218 in the revised manuscript*)

5. Images: better merge the timeline with figure 1~5 (optional).

Reply:

Thanks very much for your advice, we have merged the timeline with the newly numbered figure 6 as seen in Figure 6&7.