Subarachnoid hemorrhage in pituitary tumor

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ABSTRACT

Subarachnoid hemorrhage (SAH) is the bleeding into the subarachnoid space containing cerebrospinal fluid. The most common cause of SAH is trauma. Rupture of aneurysms, vascular anomalies, tumor bleeds and hypertension are other important etiologies. SAH in the setting of pituitary tumor can result from various causes. It can be due to intrinsic tumor related pathology, injury to surrounding the vessel during the operative procedure or due to an associated aneurysm. We discuss the pathological mechanisms and review relevant literature related to this interesting phenomenon. Early and accurate diagnosis of the cause of the SAH in pituitary tumors is important, as this influences the management.

Key words: Apoplexy, pituitary tumors, subarachnoid haemorrhage

INTRODUCTION

Tumors of the pituitary include a heterogeneous group of lesions located at sellar and suprasellar region, comprising about 10-25% of all primary brain tumors.[1] Rarely tumors of the pituitary gland can be metastatic lesion from a distant site.[2] These tumors tend to be highly vascular and often outgrow their blood supply, resulting in pituitary apoplexy characterized by necrosis, hemorrhage and sudden increase in their size.[3] Most of these bleeds, however, are intratumoral and as the pituitary gland is an extra-arachnoid structure, extension of this bleed into the subarachnoid space is rare.[4] Tumors arising from the pituitary gland extend from sella into supra- and parasellar regions, which contain major blood vessels such internal carotid artery, anterior communicating artery, anterior cerebral artery and their branches. All these vessels may be injured during the surgical removal of pituitary tumors. Association of anterior circulation aneurysms with a pituitary tumor, although rare, has been reported in the literature.[5,6] During the pituitary surgery, these aneurysms can bleed spontaneously or during manipulation. Finally, due to their high vascularity any residual tumor after surgical removal can bleed into the subarachnoid space.[7] Thus sub-arachnoid hemorrhage in pituitary tumor can result from varied causes with distinct and interesting pathogenesis.

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CLASSIFICATION

Subarachnoid hemorrhage (SAH) due to pituitary tumor can broadly be classified as

1. Pre-operative SAH - Due to pituitary apoplexy rupturing through the arachnoid into basal cistern
2. Intra-operative SAH - Due to injury to surrounding vessels and rupture of associated aneurysm
3. Post-operative SAH - Due to bleeding from residual tumor and small, minor leaking vessels.

PATHOGENESIS

Pre-operative SAH

Although pituitary apoplexy was a rare clinical entity previously, with modern neuroimaging techniques, it is being diagnosed in 1.5-27.7% cases of all pituitary adenomas.[3,8,9] It is caused by acute enlargement of pituitary adenomas due to intratumoral hemorrhage or infarction.[10] The most commonly accepted mechanism of spontaneous pituitary apoplexy is that the tumor outgrows its blood supply, resulting in ischemic necrosis and then hemorrhage.[11,12]

Although most of the cases of pituitary apoplexy develop spontaneously, there are certain precipitating factors such as

1. Pituitary hormone stimulation test[13]
2. General anesthesia
3. Estrogen and anticoagulant therapy[14]

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4. Head trauma[10,15]
5. Angiography
6. Radiotherapy (pre-operative)[16,17]
7. Bromocriptine, cabergoline therapy.[18]

A few case reports of SAH secondary to pituitary apoplexy have been published. Wakai *et al.*[9] reviewed a large series of 560 cases of pituitary adenoma who underwent surgery over a period of 30 years. Hemorrhage into the tumor occurred in 16.6% of cases, but the extension into the subarachnoid space was noticed in only 3 cases (0.5%). Kirshbaum and Chapman[19] reported a patient of acromegaly who presented with a fatal SAH due to apoplexy of an undiagnosed growth hormone secreting tumor. Beard *et al.*[20] reported a case of acromegaly in a 76-year-old female patient who presented with SAH. Mohanty *et al.*[21] reported two episodes of SAH in a case of chromophobe adenoma, which was later removed surgically. Nakahara *et al.*[22] reported a case of diffuse SAH involving sylvian fissure, basal cistern and fourth ventricle due to apoplexy in a non-functioning pituitary adenoma. Patient presented with sudden onset severe headache, nausea and vomiting simulating ruptured aneurysm. Bao *et al.*[10] reported an interesting case of pituitary incidentaloma discovered by apoplexy with SAH. The apoplectic event was preceded by head injury. They postulated that the change of blood flow in pituitary adenomas due to the fluctuations of intracranial pressure and blood pressure following severe head injury leads to the bleeding in a pituitary tumor. Satyarthee and Mahapatra[23] reported a child with pituitary apoplexy presenting with massive subarachnoid and intraventricular hemorrhage. Pituitary apoplexy in a case of Nelsons syndrome due to previous bilateral adrenalectomy for Cushing's disease 7 years prior, was reported by Gaziglu *et al.*[24] Although the pituitary adenoma is the most common type of tumor presenting as pituitary apoplexy, Tomita *et al.*[2] reported a rare metastatic pituitary tumor with sigmoid colon adenocarcinoma as the primary presenting as pituitary apoplexy with SAH. Similarly, an intraventricular craniopharyngioma presenting with SAH was reported by Kubota *et al.*[25] Zheng *et al.*[26] reported a case of pituitary apoplexy with SAH in a case of suprasellar mass who had gross hypothyroidism.

In pituitary apoplexy, blood and necrotic tumor tissue are enclosed and compressed within the confined space of the sella with the intrasellar pressure being extremely elevated. Thus, when the pressure gradient within the sella exceeds the resistance of the adjoining structures, blood from the pituitary adenomas may be expelled outside. Pituitary is an extra-arachnoid structure. The arachnoid membrane extends through the orifice of the diaphragm sellae and spreads out on the upper surface of the anterior lobe of pituitary, producing a cerebrospinal fluid (CSF) filled space called pituitary cistern. Sudden rupture of blood and tumor tissue under pressure may breach this arachnoid membrane and make its entry into the pituitary cistern. Subsequently, it communicates with basal subarachnoid space producing clinical features of SAH. It may also extend or spread into the ventricle and cerebral tissue. Wohaibi *et al.*[27] reported that the defect in the tumor capsule leads to the leakage of blood products into the subarachnoid space. Similarly, Beard *et al.*[20] observed a slit in the tumor leading to SAH at the autopsy of their patient. Since, SAH is a common clinical presentation in aneurysms, cerebral angiography is considered as the gold standard to exclude the intracranial aneurysm.

Yamada *et al.*[28] reported a very interesting case of spontaneous pituitary apoplexy who has been on steroid therapy for hypertrophic pachymeningitis. He died of subarachnoid hemorrhage with pituitary apoplexy 2 months after the admission even if there was an improvement of laboratory data and magnetic resonance imaging appearance by 1½-month steroid therapy. Autopsy revealed thickened dura mater supporting the diagnosis of hypertrophic pachymeningitis. They concluded that the inflammation of the dura caused damage to superior hypophyseal artery resulting in SAH and apoplexy in the anterior lobe of the pituitary gland. Pituitary apoplexy in a pre-existing pituitary tumor can be precipitated by pituitary provocation test. SAH in such a scenario was reported by Sanno *et al.*[29]

INTRA-OPERATIVE SAH

This group of SAH is primarily due to a vessel densely adherent to the adenoma injured due to the traction on it caused by the falling of the adenoma capsule after tumor debulking or accidental injury to a large to medium vessel in the surrounding of the pituitary adenoma. Sometimes coexisting aneurysms with the adenoma may be injured intra-operatively leading to massive hemorrhage.

Vessel injury

Pituitary tumors often extend into supra- and parasellar areas that contain a number of important vessels such internal carotid, anterior cerebral, anterior communicating and their branches. Inadvertent direct injury to these vessels during the tumor manipulation can result in torrential hemorrhage with subsequent SAH. Indirect injury to these vessels can also result due to traction during tumor decompression. Kuroyanogi *et al.*[5] reported a case of pituitary adenoma complicated by SAH, mid brain hemorrhage and thalamic infarction

during transsphenoidal surgery. There was no direct injury to any of the vessels, diaphragma sellae was not injured. They postulated that the posterior communicating artery may have been adherent to the tumor capsule and torn during tumor manipulation. A similar injury to the thalamoperforating arteries could have led to thalamic infarction.

Rupture of an associated aneurysm

Coexisting aneurysms are not uncommon with pituitary adenomas. Housepian and Pool[6] reported 32 cases of coexisting pituitary adenomas and cerebral aneurysms that had remained clinically silent out of 5762 autopsy cases. Jakubowski and Kendall[30] found 10 cases of adenoma with cerebral aneurysms out of 150 cases of pituitary adenoma studied angiographically. Out of this 7 arose from the internal carotid, 3 from anterior cerebral and one from anterior communicating artery. Wakai *et al.*[31] reported 7 cases of coincidental aneurysm in a study of 95 cases of pituitary adenoma. They stated that the incidence of aneurysms coexisting with pituitary adenomas was 7.4%, which is significantly higher than with other brain tumors (1.1%). Tsuchida *et al.*[32] found 4 cases of coincidental aneurysms, in a series of 108 cases of pituitary adenomas. Out of those, 3 were unruptured and the ruptured one was located on anterior communicating artery. All were localized to anterior circulation. Jordan and Kerber[33] reported rupture of an anterior communicating artery aneurysm coexistent with an eosinophilic adenoma of pituitary. Okada *et al.*[7] reported a similar case of anterior communicating artery aneurysm with pituitary adenoma that ruptured producing SAH. Jaunsolo *et al.*[34] reported a case of acromegaly with middle cerebral artery aneurysm presenting acutely with SAH.

There have been a few case reports of rupture of coexisting aneurysms during pituitary adenoma surgery. The cause for this is not clearly known. It may be caused by traction on the aneurysm due to sudden collapse of tumor capsule after debulking. Especially if the aneurysm or a vessel closely related to it is adherent to the tumor capsule. This is particularly important in large pituitary tumors having supra- or parasellar extensions. Liu and Yang[35] reported a series 6 cases of SAH during transsphenoidal surgery for lesions of sellar region, carried out between 1964 and 2001. Residual tumor accounted for two cases and the rest by damaged sellar and suprasellar arachnoid.

Very rarely both ruptured aneurysm producing SAH and pituitary apoplexy can co-exist. Laidlaw *et al.*[36] reported a very interesting case of SAH due to rupture of left anterior cerebral artery (A1 segment) aneurysm associated with hemorrhagic infarction of a growth hormone secreting pituitary adenoma.

POST-OPERATIVE SAH

Post-operative complications of surgery for pituitary tumors are diverse and include CSF rhinorrhea, meningitis, diabetes insipidus, septal perforation, paranasal sinusitis and visual disturbances, etc.[37] Cerebrovascular complications include pseudoaneurysm formation, carotid cavernous fistula, carotid occlusion and vasospasm. These are caused by direct injury to the intracavernous portion of the internal carotid artery. SAH following surgery for pituitary adenoma is rare and only few case reports have been published until now. Matsuno *et al.*[38] reported a case of pituitary adenoma where there was no bleeding during operation nor there was any CSF leak. However, immediately after surgery computed tomography (CT) scan showed severe SAH. Cerebral angiography failed to show any aneurysm or vascular anomalies. They finally concluded that a small branch of the internal carotid might have been adherent to tumor capsule, which was avulsed as the tumor capsule collapsed during intracapsular debulking of the tumor. In the absence of intra-operative bleeding or CSF leak direct injury to the vessel was ruled out.

Goyal *et al.*[37] reported a similar case of pituitary adenoma, which was complicated by post-operative SAH. They concluded that this may been caused by either indirect injury to a small artery caused by traction due to the descent of capsule during tumor debulking or leaking vessels of the small residual tumor. Kuroyanogi *et al.*[5] reported the case which in addition to intra-operative and early post-operative SAH due to indirect injury to an, again developed rebleeding on the 7th post-operative day. This rebleed led to SAH and mid brain hemorrhage. Ito *et al.*[39] reported a case where the transphenoidal surgery for pituitary adenoma was uneventful, however, the patient developed decreased level of consciousness after few hours and the radiology showed massive intracranial bleed and SAH. Nishioka *et al.*[40] reported post-operative vasospasm, following the transsphenoidal removal of pituitary adenoma.

The incidence of post-operative pituitary apoplexy following partial resection of a pituitary adenoma has been increasingly been reported. It was first described by Goyal *et al.*[41] It usually occurs in the immediate post-operative period (within 12 h) after subtotal resection of giant pituitary adenomas with fatal outcomes. It can occur both after the transcranial as well

as endoscopic partial resection of the pituitary tumor. Ahmad *et al*.[42] reported four cases of post-operative pituitary apoplexy, all of which had a fatal outcome, even if they were re-explored to remove the residual tumor. They concluded that a radical tumor resection must be attempted during the first surgery for giant pituitary adenomas. The case of post-operative pituitary apoplexy reported by Patel *et al*.[43] occurred in a delayed fashion on the 3rd post-operative day in a partially resected giant pituitary adenoma. Early detection and emergent endoscopic transsphenoidal exploration resulted in gross total removal of the residual tumor, decompression of the optic chiasm and a favorable neurologic outcome. Kurwale *et al*.[44] reviewed their 13 patients of post-operative pituitary adenomas over 11 years, all of which had giant pituitary adenomas. 12 patients underwent transsphenoidal excision of the tumor. Only partial excision could be achieved in all cases. Ten patients were re-explored within 24 h of the first surgery. Twelve patients died with variable post-operative course. Hypothalamic dysfunction and dyselectrolytemia were leading causes of death in nine patients, followed by meningitis and raised intracranial pressure. They advised maximum possible resection in the first operation for giant pituitary adenomas.

CLINICAL FEATURES

SAH with pituitary apoplexy

Patients in this group may or may not have previously diagnosed pituitary tumor. Previously diagnosed and symptomatic cases of pituitary adenoma may present with increasing headache, deteriorating vision, ophthalmoplegia, nausea, vomiting, lethargy or gross stuporous condition. In previously undiagnosed cases (pituitary incidentaloma) presentation is dramatic with sudden onset of symptoms. Spread of blood into the subarachnoid space produces meningismus and nuchal rigidity. There may be deterioration of visual acuity and a visual field defect. There may be also ophthalmoplegia in the form of III, IV or VI cranial palsy. Sometimes in the post-SAH period there may be residual neurological deficit such as motor paralysis, sensory deficit etc. SAH can cause vasospasm leading to ischemia of cerebral parenchyma. Majchrzak *et al*.[45] reported a case of pituitary tumor manifesting with signs of SAH and loss of consciousness. After he regained consciousness, massive left-sided paralysis was noted.

Intra-operative SAH

This group of SAH results due to either direct or indirect injury to a vessel or rupture of a pre-existing aneurysm. It presents as excessive bleeding in the operative field with unstable vitals. Even the bleeding is controlled, patient may fail to regain consciousness after recovery from anesthesia.

Post-operative SAH

Usually post-operative SAH is associated with intra-operative SAH, which has continued into the post-operative phase. However, the bleeder vessel is usually so small to be detected intra-operatively and the leaking continues producing SAH. In this scenario, patient fails to awaken from anesthesia or is disoriented. Sometimes, there may be bleeding from the residual tumor or a new bleeder in the immediate post-operative phase. This presents as normal post-operative course to be followed by decreased level of consciousness within a few hours as reported by Ito *et al*.[39] Rarely, there may be late bleeding resulting in SAH and delayed neurological deficit.[5] Post-operative hemorrhage from the residual tumor leading to SAH can give rise to symptomatic vasospasm almost similar to the ruptured aneurysm causing vasospasm.[40]

INVESTIGATIONS

CT scan

Plain CT scan in the immediate post-bleed period is the initial diagnostic tool of choice. It clearly shows the hyperdense blood in the suprasellar cistern, basal cisterns suggestive of SAH [Figure 1]. Sometimes there may be the extension of the bleed into intraventricular or intraparenchymal location. In case of pituitary apoplexy, the central necrotic part appears hypodense with the surrounding tumor appearing as an iso- to hyperdense enhancing rim [Figure 2]. Sometimes, if the enhancing part of the tumor is not well visualized and the sudden onset of pituitary apoplexy along with massive SAH in CT scan can resemble a ruptured aneurysm.[46] CT when

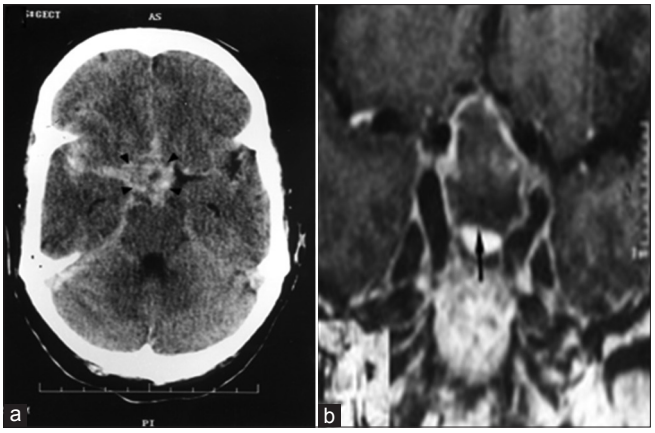

Figure 1: (a) Computed tomography without contrast, showing a heterogeneous, high density mass in the suprasellar cistern (arrowheads). There is also extensive subarachnoid hemorrhage. (b) Coronal T1 weighted magnetic resonance imaging, showing suprasellar extension of a sellar mass. The area of high intensity signal (arrow) represents methemoglobin within clotted blood. Tumor periphery appears hyperintense

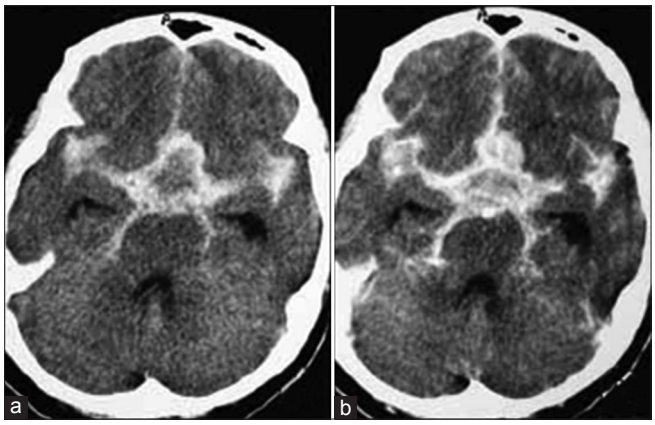

Figure 2: Computed tomography scan showing (a) Diffuse subarachnoid hemorrhage in basal cisterns, sylvian fissure. (b) Enhancing pituitary tumor

done in coronal and sagittal reconstructions are very helpful in diagnosis as it enables accurate localization of subarachnoid bleed as well as the tumor extent.

Magnetic resonance imaging

MR imaging clearly demonstrates the hemorrhage, infarction inside the tumor tissue, its extension into suprasellar and other cisterns and sometimes into the cerebral parenchyma and ventricles.

Angiography

A 4 vessel angiogram is required to properly evaluate the intracranial vasculature, not only for the recognition of relation of the internal carotid aneurysms to the pituitary adenoma but also for the detection of vascular anomalies or aneurysms. It is particularly of interest in indirect traction injury to vessels, aneurysm or other vascular anomalies in the surrounding of pituitary adenoma, producing SAH. Angiography can rule out the possibility of rupture of an associated aneurysm or vascular anomaly, which forms an important differential diagnosis in this scenario.[47] Angiography in SAH due to non-aneurysmal causes shows bilateral Gothic arch like elevation of horizontal segments of anterior cerebral arteries (A1 segment).

MANAGEMENT

SAH associated with pituitary apoplexy

Steroid replacement

Acute secondary adrenal insufficiency is seen in approximately two-thirds of patients with pituitary tumor apoplexy and is the major source of mortality associated with the condition. Corticosteroid administration is the initial measure after apoplexy.[12,26,48] Patients with pituitary apoplexy, who are hemodynamically unstable, having altered consciousness level, reduced visual acuity and severe visual field defects; should be commenced on empirical steroid therapy. In adults hydrocortisone 100-200 mg should be given initially as an intravenous bolus, followed either by 2-4 mg/h by continuous intravenous infusion or 50-100 mg six hourly by intramuscular injection. This steroid administration must be carried out after drawing blood samples for random cortisol, free T3, T4, thyroid stimulating hormone (TSH), prolactin, insulin-like growth factor-1 (IGF-1), growth hormone (GH), lutenizing hormone (LH), follicle- stimulating hormone (FSH), testosterone in men, oestradiol in women, electrolytes, renal function, liver function, full blood count and coagulation profile. Once the patient has recovered from the acute episode, the hydrocortisone dose should be quickly tapered to a maintenance dose of 20-30 mg/day, orally. Patients, who do not have acute hemodynamic or neurological symptoms, can be put on steroids if their serum cortisol is less than 550 nmol/l.

In a known hypothyroid patient, thyroid replacement and hydrocortisone should be given simultaneously.

Surgery or conservative management?

The principal controversy in management relates to the role and the timing of neurosurgical decompression [Figure 3].

- Patients with pituitary apoplexy with SAH who are without any neuro-ophthalmic signs or mild and stable signs can be considered for conservative management with careful monitoring
- Emergency surgery is required if the patient presents with severe neuro-ophthalmic signs such as severely reduced visual acuity, severe and persistent or deteriorating visual field defects or deteriorating level of consciousness should be considered for surgical management
- If the patient is stable or showing improving visual and ophthalmoplegia, initial conservative management can be adopted followed by elective tumor removal
- If there is no indication for initial operative management, it is rare to change from a conservative to an operative course. However, there is evidence that patients in whom there is no response to steroid therapy after 1 week, delayed surgical intervention may provide the benefit in terms of visual and endocrinological improvement.[49]

SAH associated with rupture of a vessel

Small vessel injury does not require any active intervention and the SAH gradually resolves with improvement of neurological status. However, one should be ready to deal with the associated complications of SAH like vasospasm.[45] In case of large vessel injury during pituitary tumor removal the injured vessel should

be repaired or ligated depending on the areas of the brain, it supplies.

SAH with rupture of an associated aneurysm with pituitary tumor

In intra-operative bleeding due to rupture aneurysm, an aneurysm can be directly clipped along with removal of the pituitary tumor, if the approach is transcranial. However, if the aneurysm can't be identified intra-operatively and the SAH is detected post-operatively, exact location of the aneurysm should be identified through angiography and then clipped.

Post-operative SAH

This is a difficult and controversial situation where the management protocol is not clearly defined. SAH resulting due to apoplexy in a residual pituitary tumor has a fatal outcome, even if managed by surgical removal of the tumor. Both Goel *et al.*[41] and Ahmad *et al.*[42] reported 100% mortality in their series of post-operative pituitary apoplexy when managed surgically. These cases, in addition to surgical removal of the tumor should be put into triple-H therapy and nimodipineto prevent cerebral vasospasm, similar to aneurysmal SAH. Routine monitoring of the cerebral blood flow velocity through transcranial Doppler and thereby identifying the vasospasm early will be valuable in decreasing the resulting morbidity and mortality.

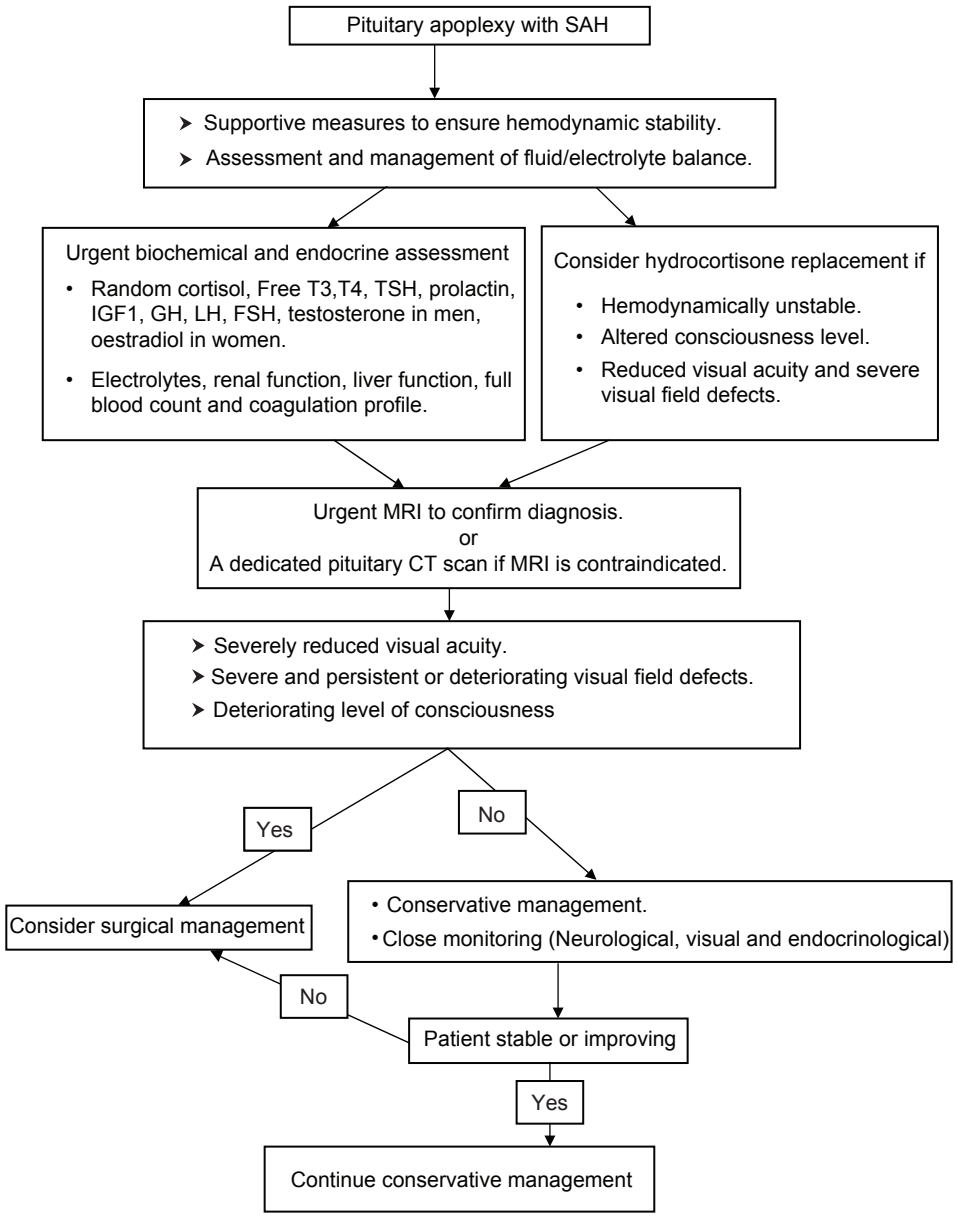

Figure 3: Flowchart depicting the management of SAH following pituitary apoplexy

CONCLUSION

SAH in pituitary tumor is a heterogenous group with many distinct and diverse clinicopathologic entities. It can range from pituitary apoplexy rarely rupturing through the arachnoid membrane into the basal cistern or due to direct or indirect injury to surrounding vessels during transsphenoidal surgery for pituitary tumors. Association of an anterior circulation aneurysm along with the pituitary tumor is not uncommon and its rupture due to direct manipulation or indirect tractional can lead to SAH. Pre-operative angiography to detect such aneurysms before pituitary surgery is advisable. CT scan in early and MRI in late stages are useful to know the cause, location and extension of such SAH. In pituitary apoplexy, complete removal of the tumor is required to improve the visual, endocrine and other neurological deficits. Associated aneurysms should be clipped to prevent the risk of rebleed. Overall the SAH in pituitary tumor requires various different kinds of management depending on its cause, which should be identified precisely and accurately.

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