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Surgical Outcome in 65 Patients of Pituitary Adenoma: Our Institutional Experience

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Abstract

We retrospectively analyzed 65 patients of pituitary macroadenomas operated in superspeciality hospital of Bangalore medical college and research institute from June 2010 to June 2016. Management of pituitary adenomas represents a significant challenge for neurosurgeons, which is further amplified by the degree of local tumor infiltration into adjacent structures such as the cavernous sinus. The goal of the treatment of pituitary tumors are improvement of the visual, endocrinological and neurological symptoms with least morbidity and acceptable cosmetic results. The aim of our study was focused on surgical outcome of four approaches that we used, that is primary transcranial (PTC), sublabial transphenoidal (SLTS), endoscopic transphenoidal (ETS) and endoscope assisted transphenoidal (EATS). *Results:* forty patients were men and 25 were women. The youngest was 10 years of age and eldest was 66 year, with mean and median age of 38 and 41years respectively. Fifty-five patients had nonfunctioning pituitary adenomas (NFAs) and 10 had hormonally active pituitary adenomas (PAs). The presenting symptoms were, visual obscuration (90.7%), headache (89%) and 7 patients had acromegaly due to growth harmone producing pituitary adenoma. Thirteen patients were operated by PTC, 30 patients by SLTS, 7 patients by ETS and 15 EATS. Gross total resection (GTR) was achieved in 70%, 42.8%, 73.8% and 46.6% patients in PTC, ETS, EATS and SLTS groups respectively. Visual improvement was seen in 70%, 42.8%, 73.8% and 46.6% of the patients in PTC, ETS, EATS and SLTS group respectively. *Conclusions:* since the goal of the treatment of pituitary adenomas are improvement of the visual, endocrinological and neurological symptoms with the lowest morbidity and acceptable cosmetic results. We suggest endoscope assisted transnasal transphenoidal approach as it combines the advantages of the stereoscopic view obtainable with a microscope and the endoscopic magnified panoramic view with best cosmetic results.

Keywords: Pituitary Adenomas; Giant Pituitary Adenomas; Transphenoidal; Endoscopic.

Introduction

Enhanced awareness of pituitary disease and the recent advances in the diagnostic technologies have contributed to the earlier recognition of PAs (pituitary adenomas). And the prevalence is about 78 to 94 cases/100,000 inhabitants and incidence rate of 4 per 100,000 [1]. Some series report a higher rate of diagnosis among women of childbearing age. However, women may not actually have a higher incidence of pituitary adenoma [2,3]. Because disruption of the pituitary axis affects reproductive capacity, women with pituitary adenomas may simply come to clinical attention more frequently than men.

Pituitary adenomas may be classified either according to their size or their functional status Those tumors that measure 10 mm or less in diameter are considered microadenomas macroadenomas are those larger than 10 mm (Fig 1). Macroadenomas may also be sub-categorized as "giant" (Fig. 2) if their

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extent reaches far beyond the normal confines of the pituitary region or their greatest diameter exceeds 4 centimeters. Pituitary adenomas may also be categorized as either hypersecretory or non-functioning.

Clinical Manifestations

Neurological Dysfunction

Neurologic signs and symptoms develop as adenomas grow beyond the confines of the sella turcica and exert pressure upon adjacent structures. As tumors enlarge, they compress the optic nerves and optic chiasm and patients experience visual deficits and diminished visual acuity. Classically this causes a bitemporal hemianopia, visual loss in the temporal fields of each eye. Tumor growth may also affect other nerves (such as the 3rd, 4th, 5th, or 6th cranial nerves) and cause facial pain and/or double vision or drooping of the eyelid. Headache, although a non-specific complaint, can occur when a tumor stretches the dural sac that surrounds the pituitary gland. Headache from pituitary lesions is usually frontal or retro-orbital and it may be bitemporal or radiate to the occipito-cervical region. Many patients will have been previously diagnosed with "migraine".

Endocrinal Dysfunction

Tumor growth impairs the normal secretory function of the anterior pituitary and causes hypopituitarism. Common complaints include diminished sex drive, fatigue, weakness, and hypothyroidism. Pituitary insufficiency generally develops slowly over time. However, acute pituitary insufficiency may occur in the setting of pituitary apoplexy, a condition in which the tumor infarcts or has internal bleeding. Apoplexy can be particularly devastating because it combines acute hypopituitarism with a rapidly expanding intracranial mass, and often causes visual loss or even sudden blindness.

The hypersecretory adenomas cause distinctive clinical syndromes that include acromegaly/gigantism (growth hormone (GH) secreting adenomas), Forbes-Albright syndrome (prolactin (PRL) secreting adenomas), and Cushing's disease/Nelson's syndrome (corticotropin (ACTH) secreting adenomas). The non-functioning adenomas (NFAs) have no known endocrine features other than hypopituitarism (decreased pituitary hormone production) and generally present either incidentally or secondary to mass effect.

Surgery

Surgery remains the first-line treatment for symptomatic pituitary adenomas as it provides prompt relief from excess hormone secretion and mass effect. Surgery is also chosen secondarily when medical treatment or radiotherapy fails; particularly for prolactin and growth hormone secreting adenomas and there is evidence to suggest that debulking of medically refractory prolactinomas and GH adenomas can return these tumors to a responsive state [4,5]. Surgery is also indicated in pituitary apoplexy with compressive symptoms regardless of the tumor type.

The minimally invasive transphenoidal approach can be used for 95% of pituitary tumors. Exceptions are those tumors with significant temporal or anterior cranial fossa extension. In such circumstances, transcranial approaches are often necessary. Occasionally, combined transphenoidal and transcranial approaches are used. Nevertheless, some surgeons extend the basic transphenoidal exposure in order to remove some of these tumors and avoid a craniotomy [6,7,8,9].

There are three basic variations of the transphenoidal approach.

1. *Submucosal transseptal approach:* The patient is placed in a lawn chair position and a hemi-transfixion incision is made just inside the nostril so that the scar cannot be seen after surgery. Most often the entire procedure can be accomplished endonasally. Conversion to a sublabial approach may be necessary for large macroadenomas and children in whom the exposure through one nostril is often inadequate. A submucosal plane is developed along the nasal septum back to the level of the sphenoid sinus. Bone of the septum is harvested for use later in the operation. The bone in front of the pituitary gland is also removed and tumor is extracted in small fragments. Afterwards the saved bone can be used to refashion the normal housing of the pituitary gland. Closure is rapid and consists of several interrupted absorbable sutures in the nasal mucosa and temporary nasal packing to promote healing of the mucosa.
2. *Septal Pushover/Direct Sphenoidotomy:* This approach uses incisions deeper within the nasal cavity. The incision for the septal pushover technique is made at the junction of the cartilaginous and bony septum. Submucosal tunnels are developed on either side of the bony septum until the sphenoid sinus is reached. Another option to reach the sphenoid sinus is by

performing a direct Sphenoidotomy. Using this method, no incision is made over septum. Instead the posterior part of septum just in front of the sphenoid sinus is deflected laterally and the sphenoid sinus is entered directly. There are several advantages to these techniques, as there is no submucosal dissection of the cartilaginous septum, the risk of an anterior nasal septal perforation is eliminated. In addition, there is less need for nasal packing postoperatively, a frequent cause of postoperative pain and discomfort. The main drawback of these more direct approaches is that the exposure is not as wide as can be achieved by the standard endonasal transseptal approach in which the cartilaginous septum can be more extensively mobilized.

3. *Pure endoscopic approach:* The pure endoscopic approach has much appeal and is being performed at selected centers. Surgery begins at the anterior sphenoid wall where a direct anterior sphenoidotomy is performed. Some surgeons prefer to perform the surgery a using a single nostril. A binostril approach, however, provides more maneuverability. To achieve an adequate exposure for the binostril approach, the septum just in front of the sphenoid sinus is removed. This allows instruments to be used in both nostrils simultaneously. Although a specialized endoscope holder may be used during tumor removal, the "3-hand" technique is advocated by many surgeons. The "3-hand" or "4-hand" technique requires two surgeons; one surgeon maneuvers the endoscope while another has both hands free to remove the tumor using microsurgical techniques. The endoscope provides panoramic magnified views of the sellar anatomy during both the approach to and resection of tumors. The option of using angled endoscopes allows surgeons to inspect for residual tumor, particularly along the cavernous sinus walls and the suprasellar region. No nasal packing is required as the procedure is performed posterior to the septum. The main disadvantages are the procedure's learning curve and that the depth of field is less easily discernible to the unfamiliar surgeon. There are 3D endoscopes that help to alleviate this potential problem

Postoperative external beam radiation therapy(RT) is highly effective in preventing recurrence of hormonally inactive pituitary adenomasas well as prevention of space occupying effects of hormonally active pituitary adenoma, but the long term biochemical remission is observed in only approximately 40% of patients, with an additional 20% requiring medical therapy [10]. Suboptimal dose(<45G) of postoperative RT has chances of late recurrences [11] and higher doses likely to end in higher chances of hypopituitarism [12,13] and infrequent CNS malignancies [14]. However with advent of GKS the function of the residual normal pituitary gland is less affected then after fractionated radiotherapy. Nonetheless, increased attention needs to be excuted to reduce the dose to the stalk and pituitary gland to minimize the incidence of these complications [15].

Material and Methods

Our study is a retrospective analysis of 65 patients of pituitary macroadenomas who required operation from June 2010 to June 2016. Of which 40 were men and 25 were women. The youngest patient was 10 years of age and eldest was 66 year, with mean and median age of 38 and 41years respectively.

The presenting symptoms (Table 1) were Visual obscuration (90.7%), headache (89%) and seven patients had acromegaly due to growth harmone producing pituitary adenoma (Table 2) of which one lady presented with dilated cardiomyopathy with ejection fraction of 22%. One patient had Cushing's disease due to ACTH over producing pituitary adenoma. Two patients presented as pituitary apoplexy with unilateral 3rd nerve palsy. Four patients presented with hemiparesis due to supradiaphragmatic extension and two had seizures.

Preoperative MRI scan (Table 3) was done in all cases, 27(41.5%) were giant (>4cms size) PAs. Of the remaining 38 PAs (<4cms size), 5 had cavernous sinus invasion (CSI), 3 had supradiaphragmatic extension and one had unilateral optic nerve encasement. Of the 27 giant PAs, 19 had bilateral CSI and 4 had unilateral CSI, 19 patients had supradiaphragmatic extension of which 4 had bilateral optic nerve encasement and 2 patients had unilateral optic nerve encasement. Obstructive hydrocephalus was seen in 3 patients of giant pituitary adenoma because of extension into 3rd ventricle.

On perimetric (Table 4) study of 65 patients, 59 presented with visual deficits. Of the 20 patients who had tumor size 1 to 2.9 cms in size, 18 had bitemporal hemianopia. Of the 18 patients who had tumor measuring 3 to 3.9cms in size, 13 patients had bitemporal hemianopia and 1 patient had temporal field cutoff in one eye with blindness is other. Of 27 giant PAs 18 patients had bitemporal hemianopia and 3 patients had unilateral temporal field cutoff with blindness in other eye, and 6 patients had blindness in both eyes.

Preoperative steroid was started in all cases and Eltroxin was started in those with hypothyroid state. In one patient of gaint hyperprolactinoma, surgery was considered as patient developed pituitary apoplexy and in this patient postoperative Cabergolin was considered. One patient of growth harmone secreting giant pituitary had dilated cardiomyopathy with ejection fraction of 22% and she needed detailed cardiac workup and was operated under high risk.

Surgery

Selection of surgical approach was based on the clinical presentation and MRI brain findings (Table 3). Thirteen patients were operated by primary transcranial approach (PTC) and the decision to select primary transcranial approach was based on transdiaphragmatic extension causing optic nerve encasement, 3rd ventricular extension causing obstructive hydrocephalus, parasellar extension into temporal lobe causing seizures and basal ganglia involvement causing hemiparesis. Nine (69%) patients developed diabetes insipidus because of pituitary stalk handling, 6 patients improved with fluids replacement and 3 were needed tablet Minrin 0.1mg daily for 3 months.

Fifty-two patients were operated by transphenoidal approach, in 30 patients microscopic TSS was done by sublabial rhinoseptal transphenoidal (SLTS) excision and septum was pushed to one side. The microscopic SLTS approach was midline, very straight approach, but had long working distance and the upper lip would obscure the visualization of upper extent in microscope.

In 7 patients endoscopic transphenoidal (ETS) excision was done through binostril approach without dissecting the cartilaginous septum and inferior turbinated was fractured on one or both sides.

In 15 patients endoscope assisted microscopic transphenoidal (EATS) excision was done through uninostril approach and only keel of vomer was excised without touching the cartilaginous septum or inferior turbinate. The initial intranasal incision was done microscopically in all cases with the help of nasal speculum through single nostril. The sphenoidal ostia was located and traced medially till keel of vomer and mucosal incision was taken and submucosal elevation of mucoperiostium was extended till the junction of bony and cartilaginous nasal septum was reached. And blades of nasal speculum was moved on either side of the keel of vomer and submucosal elevation was carried till the contralateral sphenoidal ostium was seen. The sphenoidal sinus was opened with osteotome and we noticed, that there was no troublesome bleed whenever strict submucosal plane was maintained. The mucosa of sphenoid sinus was completely debrided and hardy's speculum was introduced. The impressions of carotids in the lateral wall of sphenoid sinus was visualized on either side and was confirmed by introducing 30^0 degree scope. The floor of sella was opened under microscopic view with osteotome and roungers. The dura was opened in cruciate fashion and atraumtic ring curretes were used for tumor removal. Initial dissection was started from 2 'O' clock to 10 'O' clock in clockwise fashion and later 10 'O' clock to 2 'O' clock dissection was continued. The endoscope was introduced to check the residual tumor after microscopic debulking and gross total excision was achieved till the dome of diaphragm sella would prolapse in the sphenoid sinus. Valsalva maneuver was used to look for occult CSF leak and abdominal fat graft was inserted to plug the sella in all cases of intraoperative CSF leaks. The sella was packed with spongostan and hemostasis achieved. The bone fragments were placed in the defect and mucoperiosteal flap were repositioned and nasal cavity was packed with merocele pledgets.

Results

The surgical outcome (Table 5) of all the 4 approaches were compared. Gross total excision (Table 5) was achieved in PTC, ETS, EATS and SLTS groups in 70%, 42.8%, 73.8% and 46.6% respectively. Visual improvement in PTC, ETS, EATS and SLTS group were seen in 70%, 42.8%, 73.8% and 46.6% respectively. Vision worsened in 3 (23.1%) patients of PTC group as the cavernous sinus portion could not be addressed safely and when radical excision was attempted all 4 patients developed 3rd nerve palsy postoperatively.

The chance of CSF leak and intraoperative bleeding was comparable in all three transphenoidal groups. Two patients in ETS group developed post-operative meningitis and one patient had mortality. Postoperative diabetes insipidus was seen in 9(69.2%) patients of PTC, 1(3.3%) patient of SLTS group and 1(14.2%) patient of ETS group. The higher incidence of DI in PTC group was because of handling of pituitary stalk during radical gross total excision. Seven patients improved with fluid replacement and 2 needed long time tablet Minrin (0.1mg) once daily after discharge. The nasal continence was preserved in all cases of EATS group owning to minimal destruction of nasal septum and nasal turbinates' and also as the approach was uninostril.

The mean operative time in PTC, SLTS, ETS and EATS were 185, 85, 125 and 135 minutes respectively. The duration of postoperative hospital stay was same in all patients who improved neurologically and stay was prolonged because of complications irrespective of the approach used.

Endocrinological Outcome

Of the 7 patients of acromegaly due to GH secreting pituitary macroadenoma, 5 were gaint pituitary adenomas. All patient were operated by transphenoidal approach. In 4 patients gross total excision was possible and postoperative GH level below 5ng %(control) and in rest 3 patients GH level was above 15ng% as the intracavernous invasion could not be removed intoto, hence they were subjected to postoperative adjuvant radiotherapy. Of those patients who had hypopituitarism, amenorrhea and infertility, none improved and all needed further intense endocrinological harmone supplement. Hence surgery alone is not curative in pituitary adenoma with hypopituitarism and secretory adenoma. Multidisciplinary team approach including endocrinology and radiotherapy treatment is needed for optimal symptomatic improvement and to prevent further recurrences.

One patient of Cushing's disease due to PA, 10 year old boy was operated by SLTS approach. This patient did not have endocrinal remission and was referred to endocrinology unit for medical management. And one patient of hyperprolactinoma who presented with pituitary apoplexy was operated by EATS and was put on weekly Cabergolin is completely asymptomatic and delayed postoperative MRI scan shows to evidence of any tumor.

Only 30 patients have been following regularly. The longest follow up duration was 6 years and shortest was 3 months. There was no history of fresh worsening of vision in any patient. Of the 4 patients of GH secreting gaint pituitary adenoma, the post-operative GH level was below 8ng% (control) in two patients and less then 2ng% (cure) in two patients, but amenorrhea persisted in all and reproductive function was not corrected in one patient who had infertility. MRI brain was done in all and intracavernous residue was unaltered, otherwise there was no fresh recurrence for which surgery would be nedded.

Table 1: Showing the presenting symptoms of patients

Symptoms	Number of Patients (%)
Headache	58(89)
Visual deficits	59(90.7)
Hypopituitarism	44(67.6)
Acromegaly	7(10.7)
Hyperprolactinoma	1(1.5)
Cushings disease	1(1.5)
Hemiparesis	4(6)
Seizures	2(3)
Apoplexy	2(3)

Table 2: Showing the harmone secreting pituitary adenomas

Adenoma and Hormone Secreted	Number	Percent
Endocrine-inactive	55	84.6%
PRL	2	3%
GH	7	10.7%
ACTH	1	1.5%
TSH	0	0
Endocrine-active	10	15.4%
Total	65	-

- PRL, prolactin; -ACTH, adrenocorticotrophin; -GH, growth hormone; -TSH, thyrotrophin

Table 3: Showing the relevant MRI findings

Pituitary tumor	Number	Cavernous sinus invasion		Optic nerve encasement		Supradiaphragmatic extension	Obstructive hydrocephalus
		Unilateral	Bilateral	Unilateral	Bilateral		
1 to 3.9 CM macroadenoma	38	4	1	1	0	3	0
>4CM giant adenoma	27	4	19	2	4	19	3

CM- centimeters

Table 4: Showing visual assement of the patients

Tumor size (cm)	Cases	Blindness		Field defects (perimetry)	
		Right Eye	Left Eye	Rigfht Eye	Left Eye
1-2.9	20	0	0	18	18
3-3.9	18	0	1	14	13
>4	27	9	6	18	21
Total	65				

Table 5: Surgical outcome

	No	Average Duration of Surgery (minutes)	Extent of Excision		Visual Outcome			Post OP 3RD Nerve paresis	CSF Leak	Meningitis	DI	Nasal countenance as per patients subjective opinion	
			GTR (%)	STR (%)	Improved (%)	Worse(%)	same					Worse	Preserved
SLTS	30	85	14(46.6)	16(53.4)	14(46.6)	-	16(53.4)	0	5(16.7)	0	1(3.3)	30	0
ETS	7	125	3(42.8)	4(57.2)	3(42.8)	-	4(57.2)	0	2(28.6)	2(28.6)	1(14.2)	4	3
EATS	15	135	11(73.3)	4(26.7)	11(73.3)	-	4(26.7)	0	2	0	0	0	15
PTC	13	185	9(70)	4(30)	9(69.2)	3(23.1)	1(7.7)	4(30.8)	0	0	9(69.2)	-	-

DI- diabetes insipidus
GTR- gross total resection
STR- subtotal resection
SLTS: Microscopic sublabial rhinoseptal transphenoidal excision
ETS: Endoscopic transnasal transphenoidal excision
EATSE: Endoscope assisted microscopic transnasal transphenoidal excision
PTC: Primary Transcranial excision

Discusion

In our cases higher GTR and prompt visual recovery was observed in PTC group, as the optic nerve and optic chiasma were decompressed directly under vision, but postoperative DI wasreal problem because of handling of pituitary stalk. And when radical excision of cavernous portion of tumor was contemplated, all the 4 patients developed postoperative 3rd nerve palsy.

The chance of CSF leak and intraoperative bleeding was comparable in all three transphenoidal groups. Two patients in ETS group developed post-operative meningitis and one patient had mortality. We noticed that during endoscopic surgery the camera used to frequently get blood stained and we had to withdraw and clean with savalon gauze to clean the camera and this could have been the reason for meningitis in those 2 patients who had postoperative CSF rhinorrhea. Postoperative diabetes insipidus was seen in 9(69.2%) patients of PTC, 1(3.3%) patient of SLTS group and 1(14.2%) patient of ETS group. The higher incidence of DI in PTC group was because of handling of pituitary stalk during radical gross total excision. Seven patients improved with fluid replacement and 2 needed long time tablet Minrin (0.1mg) once daily after discharge.

Transphenoidal removal was relatively safe and effective method, even in large and giant pituitary adenomas with suprasellar extensions in most of the cases. Portion of tumor remnant or recurrent tumor in the cavernous region is real problem because invasiveness into the cavernous sinus was significantly associated with incomplete removal of the pituitary tumor. We noticed that during endoscopic surgery the camera used to frequently get blood stained and we had to withdraw and clean with savalon gauze to clean the camera and this could have been the reason for meningitis in those 2 patients who had postoperative CSF rhinorrhea. Though endoscope gives magnified panoramic view, it was not easy to achieve hemostasis when there is ongoing bleed in tumor bed and it was necessary to switch to microscope for achieving meticulous hemostasis

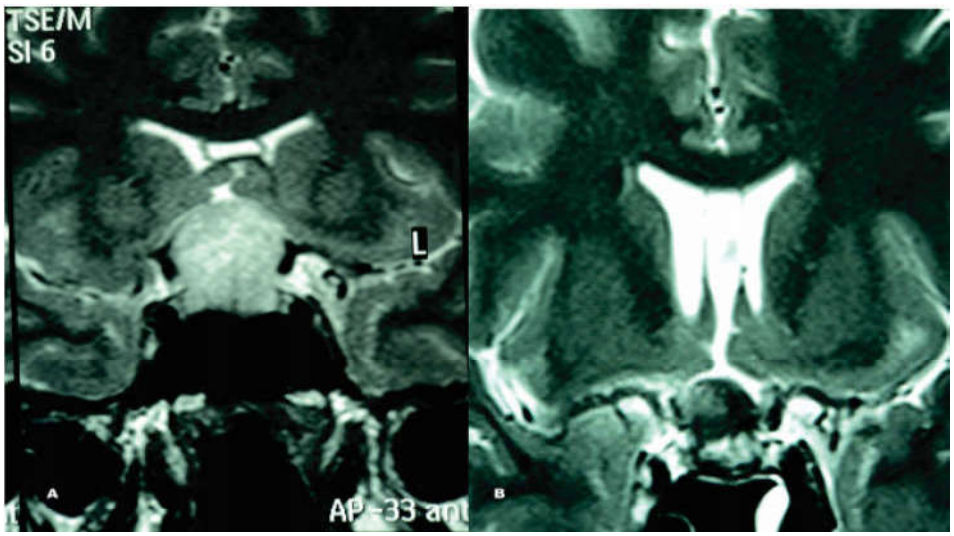

Fig. 1: MRI Brain coronal section, Inset A- preoperative scan showing pitutary macroadenoma and **Inset B-** postoperative scan,showing complete excision done through endoscope assisted transphenoidal (EATS) approach

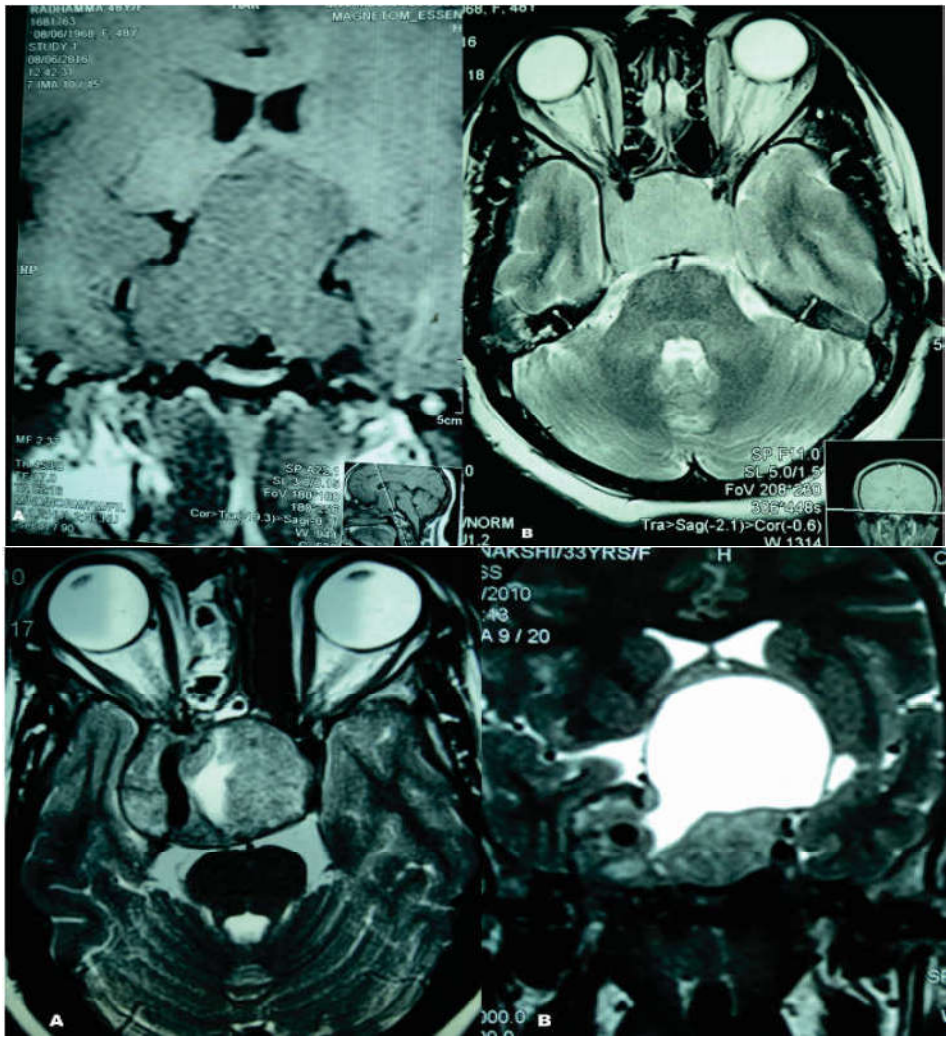

Fig. 2: T_2 W, **Inset A-** axial section showing giant pitutary adenoma with transcavernous extension into parasellar region on right side and **Inset B-** coronal section showing cystic component extending into suprasellar region with elevation of 3rd ventricle and this patient was operated by primary transcranial approach

because of the endoscope has the disadvantage of lacking the stereoscopic view obtainable with a microscope, which makes the benefits of the two techniques equivocal when comparing them in the treatment of pituitary adenomas.

EATS approach especially uninostril had the advantage of having shorter working distance when compared to SLTS approach and enjoyed the advantages of endoscopic magnified panoramic view of the sphenoid sinus where the carotid impressions were well seen and wide opening of the floor of sella could be done confidently. Also use of endoscope to check for any possible excisable residual tumor in the sella especially in 10 'O' clock to 2 'O' clock area was an added advantage which resulted in achieving highest GTR. The nasal continence was preserved in all cases of EATS group owning to minimal destruction of nasal septum and nasal turbinates' and also as the approach was uninostril.

Conclusions

Since the goal of treatment of pituitary adenomas are improvement of the visual, endocrinological and neurological symptoms with the least possible morbidity and acceptable cosmetic results. We suggest endoscope assisted transnasal transphenoidal approach as it combines the advantages of the stereoscopic view obtainable with a microscope and the endoscopic magnified panoramic view with best cosmetic results.

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