www.jmscr.igmpublication.org
Impact Factor 5.244
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i1.13

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Pituitary Tumours: A Brief Review

Authors
Himanshu Mishra[1], Ritusha Mishra[2]
[1]Senior Resident, DR RML IMS, Lucknow, U.P., India
[2]Senior Resident, IMS, BHU, Varanasi, UP, India
Corresponding Author
Dr Himanshu Mishra
154, Janki Nagar, P.O.-Bazardeeha, Varanasi, UP
Email- *hmsra1801@gmail.com, Mob- 7704909900, 8176007251*

ABSTRACT
Pituitary tumours are mostly benign tumours which constitute 10-20 % of all intracranial tumours. These may be functional (hormone secreting) or non-functional. The etiology of pituitary tumours is unknown. Incidence is common in 3rd to 5th decade of life with more predilection towards female. The frequency of various types of adenomas may vary according to type of hormone secretion, age and gender. Functional tumours produce clinical symptoms both because of hormonal dysregulation and mass effect while non-functional manifest through mass effect only. Magnetic Resonance Imaging (MRI) is imaging modality of choice. Combined modality treatment is required in the management.
Keywords- *Pituitary, Surgical resection, Stereotactic Radiosurgery.*

Pituitary tumours constitute 10-20% of all intracranial tumours. Mostly pituitary tumours are benign. Grossly they are of two types- one which produces excessive amount of pituitary hormones and other which doesn't produce any hormone. The hormone secreting tumours cause damage both by hormonal dysregulation and mass effect of tumour while that non-secreting lead to damage by local infiltration in to the surrounding structures. Pituitary tumours are more common in 3rd to 5th decade of life with female predisposition. However, the frequency of various types of adenomas vary according to type of hormone secretion, age and gender. The exact etiology of pituitary tumours is not known, however some are related to certain type of genetic abnormalities. MEN1, AIP, PRKAR1A and CDKN1B are familial pituitary syndromes found to be associated with four different genes.

Pituitary gland is situated in hypophyseal fossa which is bounded supero-laterally by dural reflections and elsewhere a depression in the body of the sphenoid bone called sella-turcica. Pituitary is a midline intracranial structure that embryologically developes from the two distinct parts of developing embryo- (1) Rathke's pouch which differentiates to form the anterior lobe of the pituitary gland called as adenohypophysis and (2) the infundibulum which gives rise to the posterior lobe of the pituitary gland known as the pars nervosa or neurohypophysis. The anterior pituitary gland produces 6 hormones i.e. thyroid-

stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH) and prolactin (PRL) while the posterior lobe secretes 2 hormones i.e. oxytocin and vasopressin or Anti-Diuretic Hormone (ADH). Actually posterior pituitary hormones are produced in hypothalamus and then passed to the posterior pituitary through hypothalamo-hypophyseal tract. Depending on the diameter of the tumour, pituitary tumours are grossly classified as microadenomas or macroadenomas. Microadenomas are tumours with diameter less than 1 cm while macroadenomas have diameter of 1 cm or greater. Macroadenomas are more common than microadenomas and have no gender predisposition, however microadenomas are more common in females.

Pituitary tumours can be functional or non-functional depending upon their secreatory activity. Patients of Pituitary tumours may present with various signs and symptoms depending upon present hormonal abnormality, size of tumour, age and gender. Regarding hormonal abnormalities, prolactinoma causes galactorrhoea, amenorrhea and infertility in females and decrease in libido, infertility and visual disturbances in males. Excessive production of growth hormone (GH) leads to acromegaly and gigantism while hypersecretion of adrenocorticotrophic hormone (ACTH) causes cushing's disease (centripetal obesity, diabetes mellitus, hypertension, osteoporosis, muscle wasting, neurological disturbances, skin abnormalities, coagulopathy and many others) and Nelson's syndrome after adrenalectomy. Thyroid-stimulating hormone (TSH) hypersecretion is manifestated by hyperthyroidism.

As far as patient evaluation is considered, complete history and thorough physical examination (with special consideration of underlying hormonal abnormality, cranial nerve involvement and visual abnormality) are mandatory. Ophthalmological evaluation (visual acquity and field vision) must be done if patient is symptomatic and in suprasellar tumours to know the baseline value so that response evaluation could be done after treatment.

Endocrinal evaluation includes blood levels of prolactin, ACTH, cortisol, TSH, free thyroxine (T4), somatomedin C (insulin-like growth factor–1 [IGF-1]), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone (exclusively in males). Complete blood count, blood chemistry assessment and urinalysis should also be done. The interpretation of these results must be done considering diurnal variations, age, gender, pregnancy, menopausal status, conditions and timing of sampling as physiological level of hormones can occur in blood and urine. Gadolinium enhanced Magnetic Resonance Imaging (MRI) is imaging modality of choice. Computed tomography (CT) is useful if patient is being planned for trans-sphenoidal surgery or when MRI is contraindicated such as in patients having pacemaker.

The aims of the treatment are maximum safe surgical resection to provide relief from mass effect, restoration of normal endocrine function and reversal of endocrine abnormality and neurological dysfunctioning.

Nonfunctioning adenomas might be microadenomas or macroadenomas, though macroadenomas are more common. Nonfunctioning adenomas induce symptoms owing to their mass effect. If nonfunctioning microadenomas are asymptomatic, they should be kept in observation. Symptomatic microadenomas should be dealt with surgery. Transsphenoidal surgery is the preferred approach. Nonfunctioning macroadenomas should be first addressed with surgery. Completely resectable tumours should be kept in observation while adjuvant radiotherapy (RT) and observation are various treatment options for residual disease. RT might be given in form of conventional fractionation or Stereotactic Radiosurgery (SRS). RT is also indicated in recurrent cases or in patients medically unfit for surgery. Various retrospective studies have demonstrated excellent local control (> 95% in 10 years) with RT dose of

45Gy/25# with conventional fractionation. SRS has also shown to be associated with very good local control rates of 92-100% at 10 years. Usually RT dose varying from 14-18.5 Gy is used for SRS.

Prolactinomas are most common functional pituitary adenomas accounting 40-45% of all pituitary tumours [(1)]. Its incidence is more common in females especially in younger age group. Prolactinoma causes amenorrhea, galactorrhea, infertility, androgenization with hirsutism and acne in females while in males it leads to libido, infertility and visual disturbances. The treatment goals are to make prolactin levels normal, restoration of reproductive function and to decrease neurological symptoms. Medical therapy is treatment of choice for prolactinomas as it not only reduces tumour size but it also brings down the prolactin level up to normal level. Dopamine agonists are used for medical treatment. Bromocriptine, lysuride or pergolide are frequently used. Bromocriptine causes normalization of prolactin hormone level in 80-90% of patients [(2)]. Cabergoline (another dopamine agonist) is better tolerated than bromocriptine but possible concern regarding its use in high doses is that it causes valvular heart disease [(3,4,5)]. For some selective patients like those having slightly raised prolactin levels and having small tumour size, medical therapy could be withdrawn at 2-3 years to assess for remission of disease. In about 8 % of cases prolactinomas are either unresponsive or intolerant to medical treatment. Dopamine agonists should not be used at the time of SRS because it has been shown that it might hamper long term efficacy [(6)].

For patients who are non-compliant, intolerant or refractory to medical treatment or have threat of rapid progressive vision loss; surgery is standard second line treatment for such cases. The long-term surgical cure rates for microprolactinomas are 50% to 60% while for macroprolactinomas are 25% (where cure is considered as normalization of prolactin levels).

Radiotherapy is considered as third line treatment strategy in management of prolactinomas. RT has its role when patients are intolerant/ non-responders to medical therapy and surgery could not be done as second line therapy. It has been shown that RT with conventional fractionation brings normal prolactin level in about 30-50% of cases. SRS could also be used instead of conventional fractionated RT since various studies have demonstrated hormonal remission rates of 18-52% with it. Study by Castinetti et al has shown it up to 43% [(7)].

Acromegaly is a rare disease characterized by hypersecretion of growth hormone (GH) and elevated levels of insulin- like growth factor-1 (IGF-1). Pituitary adenomas constitute about 95% of all acromegaly cases while rest of the cases are contributed by tumours externally secreting GH or GH- releasing hormones [(8)]. Slow progression causes delayed diagnosis [(9)]. Acromegaly apart from characteristicis bony abnormalities (involving hands, feets, frontal bone and many others) is associated with many other cardiac and respiratory disorders. The primary objectives of the treatment are to decrease tumour size, normalize IGF-1 levels as according to patient's age and gender and to decrease serum GH levels less than 1 ng/mL along with preserving adequate pituitary function.

Transsphenoidal surgery is treatment of choice for acromegaly, however multimodality approach might be required in many cases. The goals of surgery are complete removal of tumour and to alleviate mass effect. Biochemical normalization of tumour after surgery not only depends upon size of adenoma, but it also depends upon expertise of surgeon and preoperative growth hormone levels. Biochemical normalization after surgery has been found in 70-80% of microadenomas while < 50% in macroadenomas [(10,11)]. It has also been observed that GH level has reduced up to 80-90% of cases of microadenomas if the surgery has been performed by pituitary neurosurgeons [(12)]. After surgery recurrence rates are found in up to 20% of cases.

Medical therapy is required for the patients who have failed surgery, who are not fit for surgery or refractory to radiation. Medical therapy could also be used as an adjuvant treatment option after radiotherapy. Somatostatin analogs such as octreotide and lanreotide are most commonly used agents for medical therapy. They bind to somatostatin receptor subtypes 2 and 5 and cause tumour shrinkage in 30-45% cases. They are available in monthly preparations and they normalize GH and IGF-1 level in 50-70% of cases [13]. Nausea, vomiting, abdominal cramps and diarrhoea are common side effects and life- long dependence is a major disadvantage with these drugs. Pegvisomant is a growth hormone receptor antagonist which could be used as a second line drug in managementof acromegaly [14]. It is used in patients who are refractory to somatostatin analogs. It causes normalization of IGF-1 level in 90-97% of patients but life-long dependency, inability to decrease GH secretion and tumour size, tendency to derrange liver function tests and being extremely expensive make it second-line drug. Dopamine agonists such as cabergoline are less effective than somatostatin analogs and could be used in patients who are intolerant to these drugs.

RT could be considered as definitive treatment (if surgery is not feasible) or in adjuvant setting (if GH and IGF-1 levels are not normalized after surgery). RT is effective in reducing both GH and IGF-1 levels. In a large retrospective study including 884 patients, it has been demonstrated that RT resulted in normalization of IGF-1 level in 63% of cases 10 years after RT [15]. Using SRS (with peripheral doses of 20-32Gy), normalization of IGF-1 levels has been observed in 42-60% of cases [16,17]. RT with conventional fractionation usually takes a long time for hormonal remission while with SRS, it occurs comparatively earlier. SRS has also excellent local control and that's why its role as definitive treatment in management of acromegaly needs to be evaluated. However for SRS the tumour needs to be well defined and far away from optic chiasma; the factors that limit use of SRS. In view of possible suppressive effect of somatostatin analogs on RT, many clinicians used to avoid these drugs 6-8 weeks before and after RT.

ACTH producing adenoma of pituitary contributes majority of ACTH dependent cushing syndrome in adults. Cushing syndrome is manifestated by moon facies, centripetal obesity, hirsutism, acne, hypertension, diabetes mellitus, osteoporosis and many other features and it requires early prompt control. Transsphenoidal surgical resection is treatment of choice for cushing syndrome as it rapidly decreases ACTH levels. Surgery provides hormonal remission in 65-90% of cases of microadenomas, however there is 20% chance of recurrence of the disease at 10 years [18,19,20]. For the patients who could not be cured with surgery, RT is used for adjuvant treatment. RT could also be considered for definitive treatment in children (as cure rates are similar to that of surgery) and in patients who are not suitable for surgery. A study by Minniti et al has shown cortisol level remission rates of 78% at 5 years and 84% at 10 years with EBRT dose of 45 Gy [21]. However RT dose up to 54 Gy could be delivered in patients of cushing syndrome. SRS has also role in its management and many SRS studies have shown similar hormone remission rates as that with EBRT in conventional fractionation [7,22].

Medical therapy is required for the patients who are non-responders to both surgery and RT. A variety of agents capable of inhibiting steroidogenesis are used like ketoconazole, aminoglutethimide, metyrapone, mitotane and etomidate. Ketoconazole is most commonly used owing to its better tolerability and ability to be effective in about 70% of cases as monotherapy. Liver function test should be monitored while using ketoconazole as it is a hepatotoxic drug.

Bilateral adrenalectomy is also indicated in the patients who are non-responders to surgery and RT. It rapidly corrects hypercortisolism,however such patients require life long glucocorticoid and mineralocorticoid replacement therapy. Many patients undergoing bilateral adrenalectomy

develope Nelson's syndrome characterized by elevated levels of ACTH hormone, hyperpigmentation, rapid growth of the tumour and invasion in to parasellar regions. RT has role in such cases and it has been shown that SRS can result in hormonal remission in up to 36% of cases.

TSH secreting adenomas are rare as they constitute only 0.5% of all pituitary adenomas. Surgical resection is treatment of choice, but in many cases it is not possible to completely resect the tumour completely (either because size or site of tunour). Adjuvant RT and/or medical treatment is required in such cases.

TSH secreting adenomas, Pituitary carcinomas and metastasis to pituitary are rare presentations. After control of hyperthyroidism with medical therapy (somatostatin analogs or dopamine agonists) surgery is mainstay of treatment. RT could be considered for patients who underwent incomplete resection or are not candidates for surgery. Pituitary carcinomas are difficult to diagnose pathologically, hence diagnosis is made clinically. They present with manifestations of a pituitary adenoma but besides these subarachanoid space, brain involvement and distant metastases point towards its diagnosis. Despite combined modality approach its prognosis is poor. Metastases to pituitary most commonly come from carcinoma breast and lung and is difficult to resect. SRS has been tried in many such patients with median survival around 5 months.

So thus, for pituitary tumours management, combined modality approach has very important role. RT with conventional fractionation and SRS both are useful. Patients have been traditionally treated with two field (lateral parallel oppose) or three field (lataral parallel oppose with a single anerior) RT technique before the advancements in radiation therapy. SRS provides more precised treatment as compared to conventional fractionation, however its use is limited to only small tumours (of size less than 4 cm) situated 2-5 mm away from optic apparatus.

Both RT with conventional fractionation and SRS are well tolerated during therapy. Acute reactions are also minimal. Hypopituitarism (occur in 30-80% of patients within 10 years of RT) is a late complication of RT and patient may require long-term follow up with a endocrinologist and hormone replacement therapy.

Prospective randomized comparison of RT with conventional fractionation and SRS (to know which one is better in terms of efficacy and toxicity) and effect of use of radiation sensitizers with RT (to improve therapeutic ratio) could be areas for future research.

REFERENCES

1. Mindermann T, Wilson CB: Age-related and gender-related occurrence of pituitary adenomas. Clin Endocrinol (Oxf) 1994; 41:359-364.
2. Molitch ME: Pathologic hyperprolactinemia. Endocrinol Metab Clin North Am 1992; 21:877-901.
3. Webster J, Piscitelli G, Polli A, et al: A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. N Engl J Med 1994; 331:904-909
4. Schade R, Andersohn F, Suissa S, et al: Dopamine agonists and the risk of cardiac-valve regurgitation. N Engl J Med 2007; 356:29-38
5. Zanettini R, Antonini A, Gatto G, et al: Valvular heart disease and the use of dopamine agonists for Parkinson's disease. N Engl J Med 2007; 356:39-46.
6. Pouratian N, Sheehan J, Jagannathan J, et al: Gamma knife radiosurgery for medically and surgically refractory prolactinomas. Neurosurgery 2006; 59:255-266.
7. Castinetti F, Nagai M, Morange I, et al: Long-term results of stereotactic radiosurgery in secreatory pituitary adenomas, J Clin Endocrinol Metab 94:3400-3407, 2009
8. Colao A, Ferone D, Marzullo P, et al: Systemic complications of acromegaly:

epidemiology, pathogenesis, and management. *Endocr Rev* 2004; 25:102-152.
9. Katznelson L: Diagnosis and treatment of acromegaly. *Growth Horm IGF Res* 2005.
10. Fahlbusch R, Honegger J, Buchfelder M: S urgical management of acromegaly. *Endocrinol Metab Clin North Am* 1992; 21:669-692.
11. Nomikos P, Buchfelder M, Fahlbusch R: T he outcome of surgery in 668 patients with acromegaly using current criteria of biochemical "cure". *Eur J Endocrinol* 2005; 152:379-387.
12. Erturk E, Tuncel E, Kiyici S, et al: Outcome of surgery for acromegaly Perfo-rmed by different surgeons. Importance of surgical experience, *Pituitary* 8:93-97, 2005.
13. Freda PU, Katznelson L, van der Lely AJ, et al: Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. *J Clin Endocrinol Metab* 2005.
14. van der Lely AJ, Hutson RK, Trainer PJ, et al: Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 2001; 358:1754-1759.
15. Jenkins PJ, Bates P, Carson MN, et al: Conventional pituitary irradiation is effective in lowering serum growth hormone and insulin-like growthfactor-I in patients with acromegaly, *J Clin Endocrinol Metab* 91:1239-1245,2006.
16. Pollock BE, Jacob JT, Brown PD, et al: Radiosurgery of growth hormonepro-ducing pituitary adenomas. Factors associated with biochemical remission, *J Neurosurg* 106:833-838, 2007.
17. Jagannathan J, Pouratian N, Laws ER Jr, et al: Gamma knife radiosurgery for acromegaly: outcomes after failed transsphenoidal surgery, *Neurosurgery* 62:1262-1270, 2008.
18. Biller BM, Grossman AB, Stewart PM, et al: Treatment of adrenocorticotropin dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2008; 93:2454-2462.
19. De Tommasi C, Vance ML, Okonkwo DO, et al: Surgical management of adrenocorticotropic hormone-secreting macroadenomas: outcome and challenges in patients with Cushing's disease or Nelson's syndr-ome. *J Neurosurg* 2005; 103:825-830.
20. Patil CG, Prevedello DM, Lad SP, et al: Late recurrences of Cushing's disease after initial successful transsphenoidal surgery. *J Clin Endocrinol Metab* 2008; 93:358-362.
21. Minniti G, Osti M, Jaffrain-Rea ML, et al: Long-term follow-up results of postoperative radiation therapy for Cushing's disease, *J Neurooncol* 84:79-84, 2007.
22. Höybye C, Grenbäck E, Rähn T, et al: Adrenocorticotropic hormone producing pituitary tumors: 12- to 22-year follow-up after treatment with stereotactic radiosurgery, *Neurosurgery* 49:284-292, 2001.