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RESEARCH ARTICLE

CLINICAL PICTURE AND CURRENT MANAGEMENT OF PITUITARY TUMORS: A REVIEW

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Abstract

The pituitary is a pea-sized complex gland located below the hypothalamus at the base of skull in the sella turcica, is composed of three types of cells. Pituitary being the centre of all the stimulating hormones of various organs, its overgrowth leads to hormone excess syndromes, like acromegaly, Cushing disease, central hypothyroidism, and hyperprolactinemia etc. so studies involving pituitary tumors have mainly focused on hormone production. Pituitary Adenoma is the most common (~85%) tumor in the sellar-suprasellar region. Their prevalence is growing which has risen over the last 20 years probably due to improved imaging techniques and treatment outcomes. Due to the tumor's growth in size Compression of adjacent anatomical structures especially optic nerves in close vicinity can lead to focal neurologic deficits such as diplopia, visual field defects and loss of visual acuity typically bitemporal hemianopsia. The surgical procedure of choice is a trans-sphenoidal micro surgically or endoscopically performed by a neurosurgeon leaving transcranial approach for large and invasive pituitary neoplasm with sellar remnants. Even in the case of recurrent tumor or progression of residual tumor tissue after surgery, a second operation and/or radiotherapy should be considered.

Introduction:-

The pituitary is a pea-sized complex gland located below the hypothalamus at the base of skull in the sella turcica, is composed of three types of cells. First, adenohypophyseal i.e., anterior lobe hormone-secreting neuroendocrine cells. Second, Neurohypophyseal i.e., posterior lobe pituicytes that are comprised of modified glia, axonal extensions of hypothalamic neurons which secrete hormones into the bloodstream. Third are the stromal cells which include meninges, blood vessels, bone, nerves and other connective tissues [1].

Pituitary being the centre of all the stimulating hormones of various organs,it's overgrowth leads to hormone excess syndromes, like acromegaly, Cushing disease, central hypothyroidism, and hyperprolactinemia etc. so studies involving pituitary tumors have mainly focused on hormone production. However, the development of molecular tools for cell-differentiation mechanisms and transcription factors has been of great importance in better understanding and providing further clarity [2-5].

Pituitary tumorssum up for 10–15% of all intracranial neoplasms and is the third most common cranial tumor in adulthood (6,7). Pituitary Adenoma is the most common (~85%) tumor in the sellar-suprasellar region [6,7]. Their prevalence is growing which has risen over the last 20 years probably due to improved imaging techniques and

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treatment outcomes. In population-based studies, pituitary tumors were found in 77.6–115.6 persons per 1,00,000 population (8,9). The prevalence is directly proportional with increasing age and is highest between the 4th and 6th decade of life.[10] They are usually benign, with only rare exceptions, and 85% of them are pituitary adenomas (10). Hence this review aims to understand the clinical picture and management of these tumors.

Pituitary Neuroendocrine Tumors and their Clinical Picture

The clinical picture of pituitary insufficiency or hormone hypersecretion caused by a pituitary tumor generally develops insidiously over a few years [17]. Most hormones are secreted from the adenohypophysis, so the insufficiency of the anterior pituitary lobe is the most common manifestation of hormonally inactive pituitary tumors. As for pituitary macroadenomas, a representative meta-analysis [18] has found that 37–85% of patients have partial hormone deficiency on being diagnosed at the very least; the most affected cell type is somatotrophs i.e., the Growth Hormone axis (61–100% of all patients), followed by the gonadotropic axis (hypogonadism in 36–95% of all patients).

One of the common symptoms is headache which is reported in about 16–70% of patients with pituitary adenomas [19]. The gradual growth of the tumor bulk results in stretching of the diaphragm of the sella activating the fibers carrying pain sensation within the dura mater, thus leading to headache, mainly frontal and occipital regions being involved. [20] Some studies also have the view that the definitive cause of headache is not known but rarely caused by pituitary tumor [21,22]. So, it is debatable. Due to the tumor's growth in size Compression of adjacent anatomical structures especially optic nerves in close vicinity can lead to focal neurologic deficits such as diplopia, visual field defects and loss of visual acuity typically bitemporal hemianopsia [21,22].

Those patient with NFPAs or now known as PitNETs with no distinct cell lineage often present with symptoms including headache, visual defects, and hypopituitarism as they usually present late due to being hormonally inactive and express only when the tumor grows enough to show mass effect on surrounding structures. [8].

Diagnosis

Radiological-

MRI visualizes lesions in the sella turcica and the suprasellar region more accurately and better than CT and is therefore the current gold standard for the imaging of pituitary adenomas [29]. The sensitivity of MRI for microadenomas is 82.6%, compared to 42.1% for CT [30]. Snowman sign in neuroimaging which refers to the configuration of many large size pituitary Neuroendocrine tumors or previously known as Pituitary Macroadenomas. As they are soft tumors, they are indented by the diaphragm sellae both sides giving them a snowman configuration or 'figure 8' or 'dumbell' configuration. This feature helps in differentiating these tumors from meningiomas extending into pituitary fossa [31].

Ophthalmologic-

Any contact with visual pathway or optic nerves identified on imaging should be followed by an ophthalmic examination. Ophthalmic evaluation will include measurements of the visual acuity, visual field, and a funduscopic examination. Any visual impairment might not be noted by the patient due to its gradual development and can be compensated partially by the eye not affected. So, it makes it more important to evaluate[31].

Current Modalities of Management of Pituitary Neuroendocrine Tumors

Indications for surgery and Surgical Approaches

After a definite diagnosis is made, it is subjected to the question- need for surgery. The following situations are considered for surgery [28,32] -

1. Significant vision loss
2. Clinically evident increase in tumor size i.e., macroadenomas (especially if in the vicinity of critical structures, such as the visual pathway)
3. Pituitary apoplexy with potentially imminent blindness, which may constitute a neurosurgical emergency.
4. Hormonally active tumor (exception: prolactinoma, which is mainly treated with dopamine agonists)
5. Surgery can also be considered if clinically significant pituitary insufficiency is present.

Surgical approaches

The surgical procedure of choice is a trans-sphenoidal micro surgically or endoscopically performed by a neurosurgeon leaving transcranial approach for large and invasive pituitary neoplasm with sellar remnants [33].

Even in the case of recurrent tumor or progression of residual tumor tissue after surgery, a second operation and/or radiotherapy should be considered.[34].

While the endonasal transsphendoidal approach is generally considered as the gold standard for the treatment of PitNET, surgery for giant PitNET presents some important differences from surgery for smaller tumors. A gross total resection in giant PitNET after a single surgical procedure can be achieved in less than half the cases, even in specialized tertiary-care centers, while the operative morbidity and mortality rates remain high (Sinha and Sharma, 2010; Mortini et al., 2007). [35]

There are theoretical data on advantages and superiority of Endoscopic Endonasal Technique [EEA] over Microsurgical but clarity is still missing. On basis of reviews and metanalysis of individual techniques available [36-40]. Although still EEA technique supposedly achieves better results of gross total resections in macroadenomas [41-43], giant pituitary tumors [44], tumors invading the cavernous sinus [45] and in recurrent or residual Pituitary tumor [46].

Some Advantages of EEA are [47]

1. Nasal part of procedure simpler
2. Wider angle of operation
3. Safer as all structures are visualized.
4. Less traumatic
5. Less time consuming in experienced hands.

EEA is also associated with lower risks for Diabetes Insipidus, better post-surgery recovery, shorter hospital stays. Although some nasal complications like septal perforation, pain and discomfort are also seen. [39,40,48,49] Newer surgical aides such as intraoperative use of doppler, MRI, neuro navigation, improve the surgical results immensely. [50,51]

As mentioned earlier, Transcranial approaches are still done for tumors which are mainly localized or has invasion outside of the sella or if the sella turcica is unnaturally expanded irrespective of the size of the lesion. This is effective when resection becomes necessary for a part of a pituitary macroadenoma that seems to be unreachable from the transsphenoidal route because of isolation by a narrow waist at the diaphragm of sella or containment within the cavernous sinus lateral to the carotid artery or projection anteriorly onto the planum sphenoidale, or projection laterally into the middle fossa [52].

Even in patients with NFPAs, endoscopy has proven to be more efficient than microscopic surgery in terms of the quality of resection and the endocrinological outcome.[53]

Earlier, Craniotomy was thought to be the only alternative to transsphenoidal microsurgery in patients with large and asymmetrically extending suprasellar tumor components and in patients with a significantly constricted diaphragm sellae. Some of these pituitary tumors, however, can be reached and successfully removed using an extended transsphenoidal microsurgical approach [54,55].

Surgical Precautions, Complications and Outcomes

The following three anatomic concepts that are fundamental to the safe execution of a trans-sphenoidal microsurgical procedure: [56]

1. The pituitary gland is an extra-arachnoid structure.
2 The pituitary gland is strictly in the midline, with hazards to either side.
3. It is important to recognize the residual normal anterior pituitary, especially during operations to remove pituitary macro adenoma.

The cure rate in the hands of expert pituitary surgeons ranges from 80 to 90% for microadenomas and from 40 to 70% for macroadenomas with a rate of major complications below 1% [57]. However, hyponatremia may occur in up to 10%, and hypopituitarism in 7.5% of patients submitted to experience pituitary neurosurgeons [57]. The mortality rate for transsphenoidal surgery overall is lesser than 0.5% [54].

Major complications like cerebrospinal fluid leak, meningitis, stroke, intracranial haemorrhage, and visual loss, occur between 1 and 3% of operated cases. Lesser serious complications like sinus disease, nasal septal perforations,

and wound non-healing etc. occur in almost 1-7% of operated cases. The Larger the tumor and more the invasion is associated with a higher occurrence of morbidity. In recent, the aggressive extended approaches of large and invasive tumors have shown a higher incidence of CSF leak but using a pedicled nas-oseptal flap has been found effective in lowering the incidence of recurrent leaks with a success rate of almost 98.6% (58). The use of a naso-septal flap is suggested in revision surgeries for better outcomes [59]

There are two sections in which outcome can be measured after surgery for PitNETs. They are functional outcomes and oncologic outcomes. Functional goals record the symptomatic relief and improvement or preservation of pituitary and visual function, and improved quality of life [57,60]. In patients diagnosed with non-functioning pituitary adenomas, visual defects are improved by approximately 80-90%. Some visual impairment may occur or persist in 0-4%. Most patients with intact pituitary function preoperatively retain their normal function. Those with preoperative pituitary deficiency regain function in 27% of the cases. Hormone replacement therapy is advised to the remaining patients [54].

Oncologic outcomes include tumor resection, recurrence, and biochemical correction of hormone hypersecretion. Ten-year recurrence rates are approximately 16%, although it is seen that only 6% require added treatment. On long-term follow-up post-surgery, 83% of patients are alive and well without recurrence of the disease [54].

Conclusion:-

The New WHO classification for Pituitary Tumors allows easy diagnosis and individualized patient management approaches. The ideal approach to diagnosis there is an absolute need to identify the cell lineage expression of transcription factors and hormone excess.

An extensive immunohistochemistry for at least the three main transcription factors, PIT1, TPIT, and SF1; ideally, although this panel should also include ERα and GATA3. Further staining for hormonal assessments should include ACTH, GH, PRL, βTSH, βFSH, and βLH as well as the αsubunit of glycoprotein hormones (αSU), βFSH and βLH.

The absolute planning of the reaching a diagnosis, management and treatment of pituitary neuroendocrine tumors require a multidisciplinary approach which involve a team of endocrinologists, neurosurgeons, ENT, neuro-ophthalmologists and neuroradiologists with exposure and experience in pituitary diseases and surgeries. Such team will optimize the hormone levels, ophthalmological symptoms, and radiological preoperative evaluation, thus improving surgical results and minimizing the development of complications.

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