

## Anti-hormonal therapy serves as a possible treatment modality for intracranial meningiomas

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### Abstract

Meningiomas are benign, slow growing, hormone-sensitive primary brain tumours. Surgical resection is usually the definitive treatment although management of recurrent or difficult to resect meningiomas poses a challenge to neurosurgeons. Efficacy of medical therapy for meningioma has been studied widely and several retrospective and case control studies have shown contradicting results, some supporting the strong relation between increased production of reproductive hormones and tumour growth; and others not reporting any association. Randomized controlled trials (RCTs) have also not reported any statistically significant improvement while using anti-hormonal treatment for recurrent meningiomas. It is important to understand how endogenous or exogenous hormones affect tumour growth so that exact mechanism can be targeted through medical therapy.

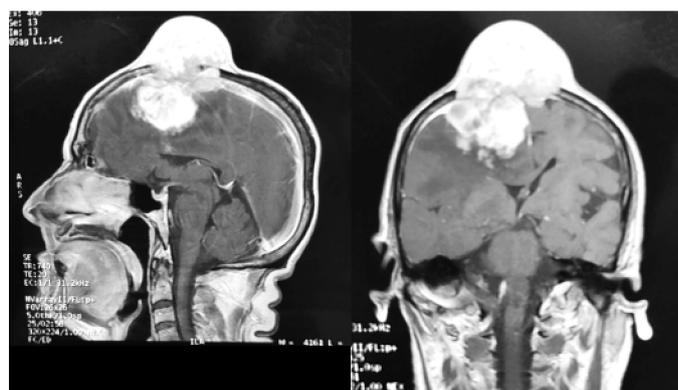
**Keywords:** Meningioma, reproductive hormones, anti-hormonal therapy, medical therapy.

### Introduction

Meningiomas arise from the meningeothelial layer of arachnoid mater and account for 20% of all intracranial tumours, making it the most common primary brain tumour. These are slow growing tumours that can remain asymptomatic. Reportedly 0.3% of the general population have an incidental finding of meningioma on neuroimaging.<sup>1</sup> Multiple etiologies for meningioma have been proposed including ionizing radiation, chromosomal deletion and uncontrolled cell multiplication due to increased production of certain endogenous hormones. The role of reproductive hormones have been studied widely in the growth of meningiomas. This association was first studied in pregnant women where the size of the tumour increased during pregnancy. Similar phenomenon was observed during breast-feeding and menstruation. Furthermore, association of breast carcinoma and spontaneous growth of intracranial lesions

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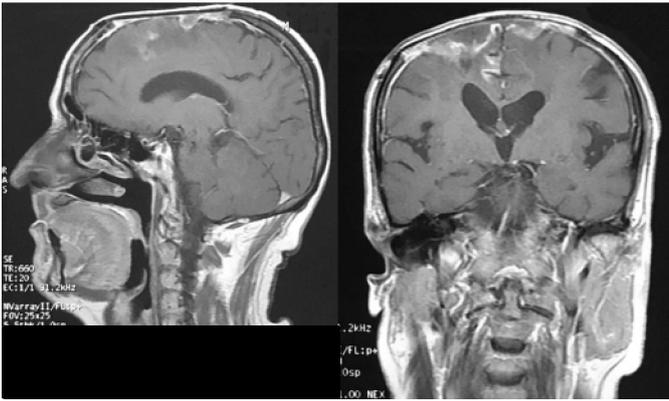


**Figure-1 (a,b):** MRI T1 post-contrast images, sagittal and coronal views showing a large meningioma with venous sinus, dura and calvarial involvement. This was a recurrent tumor that continued to grow after surgery and radiation therapy.

was also reported.<sup>1,2</sup> This led to several studies exploring the effect of hormones on tumor growth and it was hypothesized that meningioma is a hormone sensitive tumour and antagonists of these hormones can serve as a critical therapeutic role, especially for tumours that are refractory to traditional treatment modalities.<sup>1,3</sup> Molecular analysis of meningiomas later on also revealed the presence of estrogen, progesterone and androgen receptors on the tumour cells. This is similar to the concept behind the use of luteinizing hormone releasing hormone (LHRH) and cyproterone acetate (CPA) for prostate cancer.

### Review of evidence

Multiple case control studies have reported the association between meningioma growth and hormones. A case control study with the sample size of 18,037 found a positive association between hormonal replacement therapy with the incidence of meningioma (CI 2.2, 95% CI 1.9-2.6 interval).<sup>2</sup> Conversely, another case-control study done on a cohort of 10,745 individuals did not report any increased risk of meningioma among females using oral contraceptive (CI 1.15 95% CI 0.67-1.98) or low-dose CPA (CI 0.99 95% CI 0.73-1.35). However, this study showed an increased risk of meningioma among males using androgen analogues (CI 19.9 95% CI 2.81-129.74) and high dose CPA (and 6.3 95% CI 1.37-28.94). This study also



**Figure-2 (a,b):** Post-operative images of the same patient showing complete excision of the tumor, with venous sinus, dura and calvarial reconstruction.

reported that the incidence of breast and prostate cancers do not show any correlation with that of meningioma.<sup>1</sup> Few other case control studies could not find any significant role of exogenous hormones on the prevalence of meningioma in the female population.<sup>4,5</sup> Several in-vitro studies have shown the expression of somatostatin receptors on tumour surface and its critical role in regulating tumour growth. Physiologically, somatostatin inhibits release of various endogenous hormones and has an anti-angiogenesis and apoptotic characteristics which potentially inhibits tumour growth. Successful inhibition of meningioma cell growth was achieved in-vitro with somatostatin use and was reported more than 30 years ago.<sup>6</sup> In order to learn its efficacy in human subjects Johnson and his colleagues conducted a phase II randomized controlled trial to study the efficacy of subcutaneous octreotide (somatostatin analogue) in recurrent meningioma and haemangiopericytoma. Twelve patients were enrolled in the study and underwent treatment with subcutaneous octreotide, starting from 150mcg twice a day and escalating to 300mcg thrice a day, for at least 6 months. At the end of 6 months, no objective improvement in the disease process was observed. However, two patients had prolonged stability of previously progressive tumour. Side effects included diarrhoea, nausea, vomiting and transaminitis.<sup>3</sup> Mifepristone has been studied widely for its effectiveness in the treatment of meningioma. Pre-clinical studies have shown inhibitory role of anti-progesterone on meningioma cells. To re-evaluate this effect in-vivo, a phase III RCT was conducted by Ji and his colleagues in 2015. In total, 164 patients were enrolled and randomly divided into intervention and placebo arm. Eighty patients

were enrolled in the intervention arm and received oral 200 mg of mifepristone daily whereas 84 were assigned to the placebo group. They were followed over two years. Results did not show any statistically significant improvement in tumour progression. Some of the most common side effects included infections, cardiac ischaemia, thrombosis and hot flashes.<sup>7</sup>

In 2015, a literature review analyzed all the existing clinical studies on the role of Mifepristone in meningioma treatment. The endpoints included symptomatic improvement and radiological regression. The results remain inconclusive other than for its use in inoperable tumours. However, in patients with diffuse meningiomatosis, use of mifepristone has shown promising results in the preliminary evaluation.<sup>8</sup>

## Conclusion

Pre-clinical and molecular studies have shown that the tumour expresses receptors that respond to endogenous hormones. Some retrospective case control studies have also shown a positive relationship between tumour growth and endogenous and exogenous hormones, especially estrogen, progesterone and androgens. However, RCTs using the drug which blocks these hormones and hypothesized to inhibit tumour growth, have not shown promising results.

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