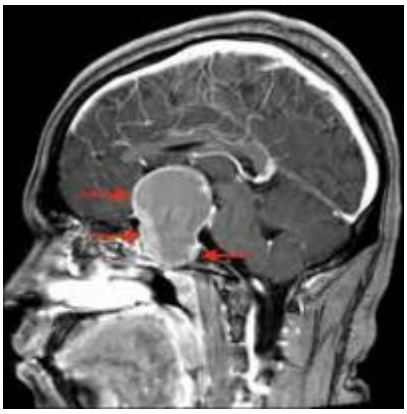
Dopamine agonist resistant lactotroph adenoma



While dopamine agonists are a primary method of therapeutic treatment for Lactotroph adenoma, the rate of resistance to these drugs continues to increase each year.

Surgery is typically indicated for patients who are resistant to medical therapy or intolerant of its adverse side effects, or are experiencing progressive tumor growth. Surgical resection can also be considered as a primary treatment for those with smaller focal tumors where a biochemical cure can be expected as an alternative to lifelong dopamine agonist treatment. Stereotactic radiosurgery also serves as an option for those refractory to medical and surgical therapy [1)].

Coopmans et al., reported a patient with an highly aggressive, dopamine-resistant prolactinoma, who only achieved biochemical and tumor control during pasireotide long-acting release (PAS-LAR) therapy , a second-generation somatostatin receptor ligand (SRL). Interestingly, cystic degeneration, tumor cell necrosis, or both was observed after PAS-LAR administration suggesting an antitumor effect. This case shows that PAS-LAR therapy holds clinical potential in selective aggressive, dopamine-resistant prolactinomas that express somatostatin receptor 5 and appears to be a potential new treatment option before starting temozolomide. In addition, PAS-LAR therapy may induce cystic degeneration, tumor cell necrosis, or both in prolactinomas [2)].

During previous long-term clinical investigations, Hu et al., from Department of Neurosurgery and Pituitary Tumor Center, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China, found that partial resistant prolactinomas exhibited significantly more fibrosis than did sensitive adenomas, suggesting a role of fibrosis in their drug resistance. Furthermore, resistant adenomas with extensive fibrosis mainly express type I and type III collagens. Since TGF-β1 is the key factor in the initiation and development of tissue fibrosis, including in the pituitary, in this study, they aimed to determine whether TGF-β1 mediated fibrosis in prolactinomas and whether fibrosis was related to prolactinoma drug resistance. Using immunochemistry and western blotting, they found that the TGF-β1/Smad3 signaling pathway-related proteins were elevated in resistant prolactinoma specimens with high degrees of fibrosis compared to levels in sensitive samples, suggesting that this pathway may play a role in prolactinoma fibrosis. In vitro, TGF-β1 stimulation promoted collagen expression in normal HS27 fibroblasts. Furthermore, the sensitivity of rat prolactinoma MMQ cells to bromocriptine

decreased when they were co-cultured with HS27 cells treated with TGF-β1. The TGF-β1/Smad3 signaling-specific inhibitor SB431542 counteracted these effects, indicating that TGF-β1/Smad3-mediated fibrosis was involved in the drug-resistant mechanisms of prolactinomas. These results indicate that SB431542 may serve as a promising novel treatment for preventing fibrosis and further improving the drug resistance of prolactinomas [3].

References

1)

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2)

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3)

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