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## Prolactinomas after bromocriptine therapy.

D B Hackney

*AJNR Am J Neuroradiol* 1986, 7 (4) 738-739

<http://www.ajnr.org/content/7/4/738.2.citation>

This information is current as  
of June 16, 2025.

# Correspondence

## CT Evaluation of Perineural Orbital Lesions

With reference to the article, CT Evaluation of Perineural Orbital Lesions: Evaluation of the "Tram-Track" Sign [1], I would like to mention that the sign at issue has already been reported on several previous occasions by Dr. E. A. Cabanis of Paris, France [2]. In particular it was widely illustrated on December 1, 1982, during the Annual Session of the French Society of Neuroradiology when the annual report, "The Orbit," was discussed in a round table session chaired by Drs. J. Vignaud and E. A. Cabanis. At that time Dr. Cabanis presented a study entitled "The Optic Nerve" and, in demonstrating the typical thickening of the optic nerve sheath in different cases (non "pathognomonic," then), he showed a picture of a Paris Tramway of the early 20th century. This communication was reported later by the author himself at the European Society of Neuroradiology, as well as in other publications in specialized journals.

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## REFERENCES

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2. Bregeat P, Bronner A, Cabanis A. "Tram-rail" image of the intraorbital part of the optic nerve by CT. *Fortschr Ophthalmol* 1982;79:32-35

## Reply

We thank Dr. Salvolini for his letter. We acknowledge that we did not cite the article by Brégeat et al. in our review of English literature as a contributor of the term "tram-track" sign. We do not take credit for coining the term "tram-track" sign, and we did include the work of Peyster et al. [1] as a contributor in their discussion of the "tram-track" sign as it relates to optic nerve sheath meningiomas.

We, however, do stand by our statement that optic nerve sheath meningiomas can be characterized by a zone of greater hyperdensity separating the low density optic nerve from the enhancing mass of the optic nerve sheath meningioma. It is this additional observation of the 'tram-track' sign which we reported and which we feel is

specific for optic nerve sheath meningiomas.

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## REFERENCE

1. Peyster RG, Hoover ED, Hershey BL, Haskin ME. High-resolution CT of lesions of the optic nerve. *AJNR* 1983;4:169-174, *AJR* 1983;140:869-874

## Prolactinomas After Bromocriptine Therapy

Dr. Weissbuch has presented an interesting set of speculations concerning the signal intensities observed on magnetic resonance images in prolactinomas after bromocriptine therapy [1]. However, it is difficult to apply his discussion to clinical cases for several reasons:

1. The precise signal characteristics to which he is referring are not illustrated. Are these changes focal or diffuse? Are the changes in signal intensity homogeneous or are there mixed areas of increased and decreased relaxation rates? Do they occur only after bromocriptine therapy or are there instances in which these changes may have been present before treatment? We have frequently observed signal intensity variations within pituitary macroadenomas and, contrary to Dr. Weissbuch's conclusions, we believe these changes represent hemorrhage, necrosis, and cyst formation [2].

2. The pathologic data reviewed do not permit one to determine whether water proton correlation times (reflecting molecular mobility) will be changed at all in treated tumors. If these changes do occur, available data do not predict whether the distribution of correlation times will be shifted toward higher or lower values. Therefore, changing the nature or structure of macromolecules within these tumors might result in increased or decreased relaxation rates. Because factors other than the distribution of correlation times contribute to determination of relaxation rates, it does not follow that since relaxation rates have been altered, correlation times must have changed.

3. Shrinkage of tumor cells without compensatory enlargement of the extracellular space will reduce the total water content of the neoplasm since the tumor will be smaller. Although this might increase the ratio of bound to free water in the tumor, it is equally possible that this ratio may remain unchanged or even decrease. If the ratio



of bound to free water is increased, the observed T1 and T2 values should be reduced. Clinical data are lacking to indicate that this effect would be sufficiently dramatic to explain the signal intensity differences observed. The changes in T1 and T2 resulting from changes of the bound to free water ratio would not explain the observation that increased signal on short spin-echo sequences may be associated with either high or low signal intensity on long spin-echo sequences. The T1 and T2 values should change concordantly if bound to free ratio changes are the mechanism.

4. Acceptance of a hypothesis that has such little empirical support is justified only if more thoroughly developed explanations are not available. Dr. Weissbuch suggests that this is the case by citing reports that indicate a very low incidence of hemorrhage in bromocriptine-treated prolactinomas. This is puzzling since hemorrhage into pituitary adenomas is a common and well-documented occurrence [3]. It is difficult to imagine that administration of bromocriptine results in resolution of preexisting hemorrhage. Was the pathologic sampling in these reports compromised by the standard practice of not submitting grossly necrotic or hemorrhagic components of the tumor for pathologic inspection?

Strong evidence for Dr. Weissbuch's hypotheses would be provided by a serial study of the evolution of signal intensity changes in prolactinomas, initially scanned before treatment, coupled with a combined surgical and pathologic search for evidence of hemorrhage. Until such data are available we will continue to consider hemorrhage a far more likely explanation for the signal intensity changes observed in pituitary adenomas because hemorrhage is a common occurrence in these tumors and the appearance of hemorrhage on MR has been well documented [4].

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2. Hackney DB, Savino PJ, Zimmerman RA, et al. Degenerative changes in pituitary macroadenomas: Documentation by MRI. Presented at the annual meeting of the American Society of Neuroradiology, San Diego, January 1986
3. Mohanty S, Tandon PN, Banerji AK, Prakash B. Hemorrhage into pituitary adenomas. *J Neurol Neurosurg Psych* 1977; 40:987-991
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#### Reply

First, I want to reiterate my desire, also, for a large multicenter, multidisciplinary, serial study of the MR-signal intensity changes in prolactinomas before and after bromocriptine therapy, correlated with medical, surgical, and pathologic data.

However, in response to Dr. Hackney's letter, I wish to say that the debate about whether bromocriptine therapy causes hemorrhage or necrosis has long been discussed in the neurosurgical and pathologic literature. Consistently, it has been shown that the pathologic

changes within prolactinomas after bromocriptine therapy consist of a continuum of unique involutional cellular and/or extracellular changes. I cited only a few of these articles [2-8]. On the other hand, hemorrhage that can be directly attributed to bromocriptine therapy has been the exception, not the rule. MR-signal changes, however, occur in about one-third of prolactinomas clinically responsive to bromocriptine therapy. Thus, hemorrhage is not a plausible explanation for the phenomenon of MR-signal changes observed so frequently after bromocriptine therapy.

Unquestionably, untreated adenomas, particularly larger macroadenomas, can manifest heterogeneous (mixed) areas of signal intensity. This can be attributed to inherent intratumoral histologic variability, hemorrhage, necrosis, and cyst formation. However, with these preexisting areas of signal-intensity inhomogeneity thoroughly noted, new distinct MR-signal changes still develop after bromocriptine administration. These MR changes may be focal, diffuse, or mixed, depending upon intratumoral susceptibility to bromocriptine, dose and length of bromocriptine therapy, and also in part to initial tumor size.

To explain how water-proton mobility relates to relaxation times, I would refer to my references 10, 11, and 13-15. Additionally, significant and consistent factors contributing to relaxation times other than water-proton mobility, such as hemorrhage, paramagnetic substances, or fat, are not supported by the pathologic changes known to occur consistently after bromocriptine administration.

My presumption that there is a secondary loss of cell water in these involuted (shrunken) cells is based on the electron microscopy studies of Rengachary and Barrow, my references 2 and 3. These micrographs show that there is a marked reduction in cytoplasmic volume, the cells appear almost desiccated. There was, in fact, about 60% reduction in cross-sectional area of cytoplasm alone. This presumption, of course, could and should be subjected to laboratory confirmation. Furthermore, it is true that the intracellular changes of decreased cell water leading to decreased water-proton mobility (increased bound to free water ratio, if you wish) would most consistently lead to shorter T1 and T2 values. However, the observation of short T1 and variable T2 values can easily be explained and understood by realizing that there is a continual fluctuation in extent and consistency of the extracellular space during bromocriptine therapy. While the primary histology within short-term-treated prolactinomas is shrunken tumor cells with only a minimal expansion of extracellular space, which would tend to suggest short T1 and T2 values, longer T2 values may be found depending upon the extent and consistency of the extracellular space. Again, as I stated, "there is a complex interplay of MR signal contributions from unique 'involutional' cellular and/or extracellular histologic changes."

My hypothesis, although speculative and unproven, however, is based on well-accepted, known histologic findings observed after bromocriptine therapy, as well as on established MR physical principles. It was my intent to enlighten my colleagues to the most plausible explanation of MR-signal changes within pituitary adenomas after bromocriptine therapy and to suggest possible implications of this phenomenon with regard to its clinical application. Further investigation is necessary, my greatest hope was to ignite it.

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