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Opinion

Explanation and Implications of MR Signal Changes within Pituitary Adenomas after Bromocriptine Therapy

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The pituitary gland has only recently been studied with magnetic resonance (MR) imaging. Initial results suggest MR may have utility in the detection and follow-up of pituitary microadenomas [1].

Of interest, it has been observed that prolactinomas treated with bromocriptine may manifest distinct and diverse MR signal changes [1]. Bromocriptine, a dopamine agonist, has been effective in the symptomatic treatment of many prolactin- and in rare instances growth-hormone-secreting tumors, causing reduction in tumor size and normalization of elevated serum hormonal levels. The apparent MR signal changes that have been observed thus far using spin-echo pulse sequencing are increased signal intensity on T1-weighted sequences suggesting shortening of T1 relaxation time and both increased or decreased signal intensity on T2-weighted sequences suggesting, respectively, prolongation or shortening of T2 relaxation time. Initial surveys suggest that about one-third of prolactinomas clinically responsive to bromocriptine manifest MR signal changes (Bradley WG Jr, personal communication).

I wish to propose an explanation of this phenomenon that considers histologic changes observed in prolactinomas responsive to bromocriptine therapy. I also wish to speculate on possible implications these MR signal changes may have in the initial diagnosis and management of prolactin- and possibly growth-hormone-secreting pituitary adenomas.

Several histologic changes are observed in prolactinomas after short-term (6 weeks) bromocriptine administration [2, 3]: (1) marked reduction in tumor cell size, primarily because of reduction in cytoplasmic volume; (2) loss of ribosomes, rough endoplasmic reticulum, and Golgi complexes (organelles related to protein synthesis); (3) clumping of nuclear chromatin; (4) increase in the number of secretory granules; and (5) increase in the number of lysosomes. Rarely, if ever, are areas of hemorrhage or infarction observed. Furthermore, there are rarely, if ever, edematous or necrotic cell changes and only a very minimal increase in extracellular space between "involuted" tumor cells observed.

Histologic changes in prolactinomas after long-term (typically over 6 months) bromocriptine therapy are fourfold [4–8]: (1) "involuted" tumor cells (as observed in short-term therapy); (2) variable number of cells showing edematous change; (3) areas of increased extracellular space such as acellular spaces filled with hyaline substance and/or degenerated necrotic tumor cells and/or inflammatory cell infiltrates; and (4) areas of fibrosis. The latter three histologic changes are observed with great variability in occurrence and extent.

Similar histologic changes have been observed in bromocriptine-responsive growth-hormone-secreting adenomas [5].

The mechanism of bromocriptine effects is uncertain. It has been conjectured that bromocriptine's effect of lowering cyclic AMP causes a reduction of exocytosis (or release) of hormone-containing granules from adenoma cells into the blood, leading to increased intracellular hormone levels, which then results, via negative feedback mechanisms, in a reduction in protein (hormonal) synthesis along with its associated cellular organelles. These involutional changes then apparently can progress to edematous cell changes, necrosis, and fibrosis

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[6–8] depending on several variables: (1) dosage of bromocriptine, (2) duration of bromocriptine therapy, and (3) differential tumor and/or intratumoral cell susceptibility. Of interest, it has been observed by neurosurgeons that prolactinomas treated before resection with short-term bromocriptine are often "softer and more fluid" and tend to be more easily suctioned than those with no prior treatment [3]. Unsuctionable and apparently fibrotic areas can be encountered after long-term therapy [3, 6, 9].

With all the above stated, how can these bromocriptine-induced histologic changes explain the MR signal changes observed? To begin, any tissue has MR relaxation times that are a composite of T1 and T2 values of the heterogeneous proton environment contained within it. In healthy, viable tissue, cytoplasmic water and more specifically its mobility is thought to contribute the most to MR relaxation times of the gross tissue [10, 11]. Increased intracellular molecular mobility correlates with decreased cellular structure.

Molecular mobility can be quantified by the average frequency of molecular collisions. The shortest T1 value occurs when the molecular mobility is such that the frequency of water-proton collisions is equal to the frequency of precession, the Larmor frequency, while greater or lesser degrees of mobility will result in longer T1 values. Thus, increasing molecular mobility can either shorten or prolong T1 values depending on what the initial molecular mobility was relative to the Larmor frequency. T2 values are consistently prolonged as mobility increases, since proton spins dephase or become incoherent less rapidly because the increased molecular motion results in canceling or averaging out local, internal molecular magnetic field inhomogeneities [12–14].

As a technical note, it is important to emphasize that Larmor frequency is dependent on external magnetic field strength. Thus, different field strength magnets will modify T1 values. In general, increasing field strength prolongs T1 values. T2 values are much less field-strength dependent [12]. These facts underscore the need to do serial studies of tumors using the same magnetic-field-strength magnet (preferably the same magnet) as well as the same pulse sequence and parameters, in order to establish "true" MR signal change. Also, if different field-strength magnets are used, T2 and not T1 values will be more indicative of true change.

In concurrence with theory, it has been empirically found that "healthy" tissues (normal or neoplastic) that contain relatively large percentages of cell water have relatively longer T1 and T2 values than those containing less water, which have relatively short T1 and T2 values [10, 15].

However, both short- and long-term bromocriptine-treated prolactinomas contain rather unique cells; they are "involuted." The most pertinent features of these involuted cells to be considered are twofold: (1) marked reduction in size, primarily due to reduction in cytoplasmic volume, thereby increasing also the number of cells per unit volume of tissue, (2) deterioration of *intracellular* environmental structure due to decreased protein synthesis with subsequent decrease of complex proteins, macromolecules, and complex nuclear and cytoplasmic structures. Feature 1 would tend to decrease overall cell and tissue water, which, as mentioned, usually is associated with relatively short T1 and T2 values. But also to be considered is feature 2, which in theory could contribute toward increased intracellular molecular mobility and therefore contribute toward either shortening or prolongation of T1 and prolongation of T2 values.

The MR signal changes observed in short-term bromocriptine-treated prolactinomas, which contain uniform populations of these involuted cells, should be almost completely attributed to the effects of these unique cell features.

The MR signal changes observed in long-term bromocriptine-treated prolactinomas, however, must in addition consider MR signal contributions from (1) edematous and necrotic cells, (2) the extracellular space, and (3) fibrous tissue, all of which occur in variable amounts:

1. Edematous or necrotic cells have an intracellular milieu that is in effect "watered down." This leads to overall increased molecular (water) mobility which again can either shorten or prolong T1 and prolong T2 values.

2. The extracellular spaces contain large amounts of water, much of which is in hydration layers around proteins that have leaked into the extracellular space from necrotic cells and plasma. Hydration-layer water has less mobility, and therefore shorter T1 and shorter (though still long) T2 values, relative to bulk water. In general, increased extracellular space, depending on its extent and consistency, leads to variable T1 value changes and longer T2 values within the overall tissue [11].

3. Fibrous tissue for the most part has a paucity of mobile water and therefore contributes a lack of MR signal.

Thus, the MR signal changes (or for that matter the lack of change) in prolactinomas clinically responsive to bromocriptine can be explained by a very complex interplay of MR signal contributions from unique "involutional" cellular and/or extracellular histologic changes.

There are several possible implications of these MR signal changes seen in pituitary adenomas after bromocriptine administration:

1. Classification of pituitary adenomas via bromocriptine effect on their MR signal. The clinical utility of such a classification is uncertain. Initial surveys suggest that only about one-third of prolactinomas clinically responsive to bromocriptine do in fact manifest MR signal changes.

2. Those pituitary adenomas in which definite MR signal changes have been observed can be monitored closely. The evolution of signal changes while on bromocriptine therapy can be correlated with clinical response and/or tumor consistency and histology found at surgery. Perhaps an analysis of this data could establish certain patterns of MR signal change that will serve as useful guideposts for medical and/or surgical management.

3. In addition, those patients who have strong clinical evidence for a prolactin- (or growth-hormone-) secreting pituitary adenoma, but show no definite signs or equivocal signs of a microadenoma on initial CT or MR and yet are clinically responsive to bromocriptine, perhaps should be restudied with MR after short-term therapy, looking for a telltale area of MR signal change within the pituitary gland. Of course paramagnetic contrast agents may prove to play a major role in detecting those tumors undetectable by CT and nonenhanced MR.

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