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Characteristics of Dynamic Magnetic Resonance Image Enhancement in Prolactinomas Resistant to Dopamine Agonist Therapy

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Abstract

Objective—To determine whether dynamic magnetic resonance imaging (dMRI) enhancement parameters could predict dopamine agonist (DA) resistance in prolactinomas.

Methods—We retrospectively identified patients with prolactinomas who were treated with DA and underwent dMRI from 2001 through 2012 at Mayo Clinic (Rochester, Minnesota). Intensities of the adenoma and pituitary gland were measured by drawing regions of interest on the images. Enhancement ratio, enhancement peak, prepeak slope (PPS), and enhancement time were compared between DA-resistant and DA-responsive groups, between DA-treated and DA-naïve groups, and between the first and follow-up dMRIs.

Results—We identified 49 patients with prolactinomas, with 6 (12.2%) that showed DA resistance. Thirty-seven patients (75.5%) underwent dMRI while receiving treatment, 12 (25.5%) underwent dMRI before starting therapy, and 10 (20.4%) had follow-up dMRI after DA therapy. The PPS of the tumor was higher in the treatment-resistant group vs the responsive group (mean [SD], 4.42 [3.19] vs 2.65 [1.59]; $P=.03$), whereas no difference was noted in the pituitary gland (5.79 [2.21] vs 4.06 [2.48]; $P=.11$). Logistic regression analysis indicated that tumor PPS was associated with DA resistance (odds ratio, 1.71; 95% CI, 1.07–3.27; $P=.02$).

Conclusions—dMRI with PPS analysis potentially can be used early in the treatment course to evaluate DA resistance in pituitary prolactinomas.

Keywords

lactotroph adenoma; magnetic resonance imaging; neurotransmitter agents; pituitary neoplasms

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Introduction

Prolactin (PRL)–secreting pituitary adenoma is the most common subtype of pituitary adenomas and represents about 40% of all pituitary lesions (1-3). First-line therapy is with dopamine agonists (DAs), including bromocriptine and cabergoline, which reverses clinical symptoms, normalizes PRL levels, and reduces tumor size for most patients (1,3-5). However, primary resistance to DA has been reported in up to 10% to 18% of treated patients, depending on how resistance is defined in the studies (1,6,7). Men more frequently have DA resistance than women (8). Resistance also occurs more frequently in patients treated with bromocriptine than cabergoline (25% vs 10%, respectively) (9,10). The definition of resistance varies. In cases of medication intolerance or tumor resistance to DA therapy, transsphenoidal surgery is considered the second-line therapeutic option. In specialized centers, published surgical remission rates for microprolactinomas after PRL level normalization are 75.9% to 91.3% (11,12). Conventional radiotherapy and stereotactic gamma-knife therapy usually are reserved for when dopamine agonists and surgery do not result in remission (13,14). Identifying tumors with DA resistance would be beneficial because patients would not have to endure a prolonged therapeutic trial before considering alternative therapeutic modalities. However, DA resistance currently cannot be predicted.

Dynamic magnetic resonance imaging (dMRI) has been used in the diagnosis and localization of pituitary microadenomas. A previous study of prolactinomas showed that marked changes in tumor enhancement after short-term DA therapy could be seen with contrast-enhanced dMRI (15). Currently, it is unclear whether DA-resistant and DA-responsive tumors differ in terms of postgadolinium enhancement characteristics. Therefore, we analyzed several dMRI enhancement parameters from a series of prolactinomas to identify any changes that might predict tumor resistance to DA.

Materials and Methods

Subjects

This study was approved by the Mayo Clinic Institutional Review Board. The institutional radiology database was searched to identify patients with pituitary prolactinomas that were visible lesions on dMRI. Patients were seen from January 1, 2001, through December 31, 2012. The diagnosis was confirmed clinically and biochemically (elevated PRL with symptoms of galactorrhea, oligomenorrhea, amenorrhea, or male hypogonadism). Patients who had been treated with radiation or surgery and whose tumors were not visible on dMRI were excluded. Clinical data collected included symptoms, laboratory testing, treatment, duration of therapy, and elapsed time between repeated imaging and response to medical therapy. Resistance to DA therapy was defined as a failure to achieve a normal PRL level on maximally tolerated doses of DA and a failure to achieve a >50% reduction in tumor size (1).

PRL Assay

PRL in serum was measured with an immunoenzymatic assay (DXI 800; Beckman Coulter, Inc). Reference ranges were 3 to 13 ng/mL for males and 3 to 27 ng/mL for females. The

analytic measuring range for the PRL assay was 1.0 to 160 ng/mL (up to 100-fold dilutions were acceptable) and the coefficient of variation (CV) for assays was <5% at all concentrations of quality-control material used to monitor stability of assay performance (4.6 ng/mL, 4.5% CV; 15 ng/mL, 3.6% CV; 32 ng/mL, 4.3% CV). Serum PRL was the first measurement obtained at the first clinical visit.

Magnetic Resonance Imaging

As described previously (16), images were acquired with 1.5T (60%) or 3T MRI (40%) with thin (3 mm) coronal sections through the sella before and after gadolinium contrast. The protocol included a dynamic T1-weighted fast spin-echo sequence through the sella during the injection of 10 mL gadolinium, followed by 40 mL of normal saline at a standard rate of 3 mL/second, with 4 sections through the sella (acquired every 20-30 seconds). This sequence was (repetition time)/(echo time)=400/minute full echo fast spin-echo sequence, with an echo train length of 3, a slice thickness of 3 mm, and an 0.3-mm interslice gap.

Sequential Quantification of Enhancement Curves in Dynamic Images

As described previously (16), the intensities of adenoma and pituitary gland in subjects at each time point in the sequence were measured by drawing a region of interest (ROI) that included as much of the tumor as possible on the pituitary adenoma and a matching or larger normal anterior lobe pituitary gland on the dynamic sequence image that best demonstrated the tumor, as shown in Figure 1. The ROIs were manually traced by one trained reader, with a review of all ROIs by the expert neuroradiologist who designed the program. Those ROIs were then propagated to the images at the same location but at other time points in the dMRI acquisition and the respective mean intensities were calculated using custom software. Sequential quantification of dynamic images included the following calculations:

1. Enhancement ratio (ER), defined as the ratio of intensities at time t compared with baseline; $ER = P(t)/P(0) \times 100$ or $A(t)/P(0) \times 100$, where $P(t)$ is the intensity of the pituitary gland at time t ; $P(0)$ is the intensity of the pituitary gland at time 0; and $A(t)$ is the intensity of the adenoma at time t .
2. Enhancement peak (EP), defined as the highest enhancement intensity of the pituitary gland or adenoma.
3. Prepeak slope (PPS), defined as the enhancement rate just before reaching peak intensity and calculated as $PPS = (E1 - E2)/(T1 - T2)$, where $E1$ is >75% peak intensity of the pituitary gland or adenoma; $E2$, intensity at time before $E1$; $T1$, time of $E1$; and $T2$, time of $E2$.
4. Enhancement time, defined as the relative time that adenomas reached their peak enhancement relative to the normal gland (ie, early, simultaneous, or late).

Data Analysis

Quantitative clinical and biologic variables were described with mean (SD) and categorical variables were compared by percentage. Variable analyses between resistance and response groups and between DA-treated and DA-naïve groups included the Student t test, Wilcoxon rank sum test, and the χ^2 test, whereas analyses between the first MRI and follow-up MRI

used the paired Wilcoxon signed rank test. Statistical analyses were conducted using the JMP 9 package (SAS Institute, Inc). Logistic regression analysis was used to evaluate factors associated with resistance to DA therapy. A 2-tailed P value $<.05$ was considered to indicate statistical significance.

Results

Clinical and MRI Characteristics

We first identified 58 cases of pituitary prolactinomas with visible lesions on dMRI. All patients were receiving care from an endocrinologist. Of the 58 patients, 49 were treated with DA and were included in our study (44 with microadenomas and 5 with macroadenomas). Twelve patients (24.5%) had no DA exposure before dMRI (DA-naïve group) and 37 (75.5%) received DA before dMRI (DA-treated group). Six cases (12.2%) were classified as having resistance to DA (bromocriptine [$n=3$]; cabergoline [$n=2$]; both [$n=1$]), and the remaining 43 (87.8%) were classified as responders (Table). All patients with resistance were in the DA-treated group, and 4 of the 6 patients with resistance did not respond to either bromocriptine or cabergoline. Among the 49 cases, 10 (20.4%) had follow-up dMRI after a mean (SD) treatment duration of 1.99 (1.61) years; the others underwent standard pituitary imaging follow-up.

Baseline characteristics of the entire sample are presented in the Table. We observed no differences between the responsive and resistant groups or between the DA-naïve and previously treated groups before dMRI in terms of age, sex, body mass index, medication category, serum PRL, follow-up time, tumor size, and tumor location on MRI. The DA-resistant group received therapy for a significantly longer length of time.

Enhancement Curves of dMRI Based on Responsiveness to DA

The EP of the pituitary gland was much higher than that of the tumor in each group ($P<.001$) (Figure 2, left). There were no differences in pituitary gland EP (mean [SD], 586.43 [310.49] vs 739.39 [197.95]; $P=.25$) and tumor EP (438.72 [31.80] vs 489.31 [85.13]; $P=.58$) between the responsive and resistant groups. The PPS of the pituitary gland was higher than that of the tumor in the responsive group ($P<.001$), but no differences were observed in the resistant group ($P=.70$). The PPS of tumors was higher in the resistant group compared with the responsive group (mean [SD], 4.42 [3.19] vs 2.65 [1.59]; $P=.03$), whereas no difference was seen in pituitary glands (5.79 [2.21] vs 4.06 [2.48]; $P=.11$) (Figure 2, right). The enhancement time was not different between the resistant and responsive groups ($P=.94$).

Logistic regression was used to explore the factors contributing to DA resistance or response. Tumor PPS (odds ratio [OR], 1.71; 95% CI, 1.07-3.27; $P=.02$) and medication duration (OR, 1.26; 95% CI, 1.00-1.64; $P=.04$) were significantly associated with DA resistance, but medication category (bromocriptine, cabergoline, or both) was not ($P=.64$).

Enhancement Curves Based on DA Treatment Before dMRI

Parameters of dMRI for DA-naïve (n=12) and DA-treated patients (n=37) were compared. As shown in Figure 3, the EP and PPS in the pituitary gland were significantly higher than those of the tumor both in DA-naïve and DA-treated groups. No significant difference was observed between DA-naïve and DA-treated patients regarding the EP or PPS for the pituitary gland or the tumor.

Enhancement Curves in dMRI Before and After Treatment

Among the 49 patients with prolactinomas, 10 (20.4%) underwent MRI before and after treatment (mean [SD] treatment duration, 1.99 [1.61] years). This group consisted of 8 women and 2 men with a mean (SD) age of 38.60 (12.93) years and a mean (SD) tumor size of 5.80 (1.47) mm.

The enhancement ratio curves of pituitary gland and tumor before and after DA treatment were compared (Figure 4). PPS was similar before and after therapy in the pituitary gland (mean [SD], 4.48 [2.00] before therapy vs 3.62 [1.90] after therapy; $P=.28$) and in the tumor (2.88 [1.81] vs 2.20 [1.88]; $P=.32$). Not surprisingly, the PPS of pituitary gland was higher than that of the tumor in the first MRI ($P=.049$) and in the second ($P=.01$). No significant difference was observed between the first and second MRI regarding the EP (mean [SD] for pituitary gland, 764.94 [100.94] vs 609.45 [100.94]; $P=.29$; for tumor, 531.89 [83.07] vs 407.04 [83.07]; $P=.30$).

Discussion

In the current study, we used dMRI to compare enhancement parameters between DA-resistant and DA-responsive prolactinomas. Patients in the resistant group had a significantly higher tumor PPS, whereas other parameters such as EP and enhancement ratio time were not significantly different between groups. Logistic regression analysis demonstrated that tumor PPS was the only significant predictor of resistance to DA. The higher PPS was seen in DA-resistant tumors, even when these patients were already receiving DA therapy at the time of dynamic MRI. Although all DA-resistant prolactinomas were initially treated with bromocriptine, the majority (4 of 6) also were treated with cabergoline and resistance persisted. Treatment type was not a significant predictor of resistance to DA with statistical modeling.

Our findings agree with the previous study of microcirculation imaging in prolactinomas, which correlated changes in vascularity with medical treatment (17). Manuchehri et al (15) studied 11 patients with microprolactinomas and 23 with macroprolactinomas by using contrast-enhanced dMRI to explore whether DAs cabergoline and quinagolide exerted their effects through changes in tumor functional vascularity. They reported that vascular parameters (enhancement index) decreased in prolactinomas after DA therapy and that the functional vascularity of prolactinomas differed from that of the pituitary gland with regard to vessel permeability and response to DA, indicating that the vessels may have fundamentally altered during tumor angiogenesis. Our finding of higher PPS in normal pituitary compared with the adjacent prolactinomas is also consistent with a previous report

that used immunohistochemical staining for vascular endothelial growth factor to demonstrate significantly higher vascularity of normal pituitary glands compared with adenomas (18).

In contrast to the technique used in Manuchehri et al (15), which is somewhat challenging to perform in routine clinical practice, the dMRI vascular parameters in this study can be measured using standard clinical dMRI protocols. We also have expanded the potential application of vascular parameters to not only demonstrate changes in tumor vascularity after therapy but also potentially predict tumor resistance to therapy. Specifically, PPS may be the best candidate to indicate DA response. The persistently higher PPS, as shown by dMRI after DA treatment, would suggest resistance to DA therapy and earlier consideration of other treatments.

We also compared enhancement curve parameters of patients before and after treatment with DA to indirectly study the vascularity changes associated with DA treatment. Although the PPS and EP were not significantly different between DA-naïve and DA-treated patients, PPS was higher in the pituitary gland and tumor in the DA-naïve group. Of the patients who had follow-up dMRI, PPS of the enhancement curves decreased after DA treatment for the pituitary gland and tumor, although again, this was not a statistically significant difference. We posit that the tendency toward decreased EP and PPS after DA treatment reflects the antiangiogenic effect of DA. In other words, DA may cause prolactinoma shrinkage by changing the functional vascularity of the tumor. DA selectively inhibits vascular permeabilizing and angiogenic activities of vascular endothelial growth factor, which is mediated through D₂ receptors (19). Therefore, DAs potentially have an inhibitory effect on vascularity through inhibition of sensitivity to vascular endothelial growth factor, a mechanism supported by the findings of McCabe et al (20).

We recognize limitations of the current study, including retrospective characterization and the relatively small number of subjects with resistant tumors. However, the number of patients with resistant disease reflects previous reports (12% vs 10%-18%) (1,6,7). We anticipate seeing a greater difference in enhancement between resistant and responsive tumors in a larger sample of patients, especially including patients with less complex disease not referred to a tertiary care center. Tumors that are easier to differentiate from normal pituitary and more responsive to therapy would presumably have even lower PPS after treatment compared with resistant prolactinomas.

In summary, our study demonstrated that prolactinomas with resistance to DA had a higher PPS in a dMRI study compared with prolactinomas that showed a clinical response. Importantly, this characteristic could be used to predict resistance even after the tumor was treated with DA. Future prospective studies of pituitary enhancement characteristics during dMRI could help facilitate earlier identification and management of treatment-resistant prolactinomas. In addition, earlier identification of tumors more likely to be responsive to DA therapy and remain in remission could potentially result in earlier withdrawal from DA. The technique of measuring enhancement characteristics could be an important noninvasive method in diagnostic and management strategies for prolactinomas.

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Abbreviations

CV	coefficient of variation
DA	dopamine agonist
dMRI	dynamic magnetic resonance imaging
EP	enhancement peak
ER	enhancement ratio
OR	odds ratio
PPS	prepeak slope
PRL	prolactin
ROI	region of interest

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Figure 1.

Left panel, The prolactinoma and matching pituitary lobe on the dynamic sequence image that best visualized the tumor. Right panel, Example regions of interests. L indicates left; R, right.

Figure 2.

The enhancement peak (EP; left panel) and prepeak slope (PPS; right panel) enhancement curves in patients with dopamine agonist (DA)- responsive tumors (n=43) and DA-resistant tumors (n=6). Data are expressed as mean (standard error).

Figure 3.

The enhancement peak (EP; left panel) and prepeak slope (PPS; right panel) of enhancement curves in patients with dopamine agonist (DA)–naïve and DA-treated disease. Data are expressed as mean (standard error).

Figure 4.

The enhancement ratio (ER) curves (left panel) and prepeak slope (PPS) (right panel) of pituitary gland and tumor in basal and follow-up dMRI. Data are expressed as mean (standard error).

Table
Clinical and MRI Data Stratified by DA Sensitivity and DA Treatment Status Before dMRI

Characteristic ^a	Total (N=49)	DA Sensitivity		DA Treatment Status		
		Responsive (n=43)	Resistant (n=6)	Treated Before dMRI (n=37)	Naïve to DA (n=12)	P Value
Age, y	38.4 (11.8)	39.0 (11.4)	34.8 (15.1)	40.0 (11.3)	33.7 (12.5)	.11
Female sex, No. (%)	39 (80)	34 (79)	5 (81)	28 (76)	11 (92)	.23
Body mass index, kg/m ²	27.0 (6.61)	27.1 (6.68)	26.6 (6.66)	27.11 (7.21)	26.6 (4.49)	.82
Initial serum prolactin, g/dL	175 (207)	155 (129)	314 (480)	192 (229)	124 (108)	.33
Medication, No. (%)						.24
Bromocriptine	19 (39)	16 (37)	3 (50)	16 (43)	3 (25)	
Cabergoline	27 (55)	25 (58)	2 (33)	18 (49)	9 (75)	
Both	3 (6)	2 (5)	1 (17)	3 (8)	0 (0)	
Therapy length, y	4.51 (4.03)	4.00 (3.93)	8.16 (2.85)	5.06 (4.19)	2.81 (3.06)	.09
Follow-up period, y	7.61 (6.69)	7.15 (6.99)	10.8 (2.60)	8.10 (7.46)	6.13 (3.30)	.38
Maximum tumor diameter, mm	6.32 (3.35)	6.20 (3.27)	7.16 (4.11)	6.08 (3.48)	7.08 (2.90)	.37
Location on MRI, No. (%)						
Left	22 (45)	18 (42)	4 (67)	16 (43)	6 (50)	NS
Right	17 (35)	15 (35)	2 (33)	13 (35)	4 (33)	NS
Middle	10 (20)	10 (23)	0 (0)	8 (22)	2 (17)	NS

Abbreviations: DA, dopaminergic agonists; dMRI, dynamic magnetic resonance imaging; MRI, magnetic resonance imaging; NS, not significant.

^aData shown are mean (SD) unless otherwise indicated.