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ORIGINAL ARTICLE

T2-weighted magnetic resonance imaging characterization of prolactinomas and association with their response to dopamine agonists

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Abstract

Purpose Recent work supports the use of T2-weighted MRI intensity as a tool for treatment stratification in acromegaly. Our study aimed to establish if the pattern of T2 intensity could be a predictor of hormonal and/or tumoral response to dopamine agonists (DAs) in prolactinomas.

Methods This was a retrospective study performed in two academic centers. We characterized the magnetic resonance T2-weighted aspect of prolactinomas (signal intensity and homogeneity in the whole tumors) before DA therapy and correlated this pattern to the prolactin (PRL) concentration at diagnosis and to hormonal and tumoral responses after 1 year of medical treatment. We separately analyzed a subgroup of prolactinomas visually very bright in more than 50% of the surface ("cystic" tumors).

Results Out of 70 prolactinomas, 80% were T2 hyperintense and 40% were heterogeneous. At diagnosis, heterogeneous prolactinomas were more frequent in men (68% vs. 28.9%, $p \le 0.011$), larger (median area 304.5 mm^2 vs. 56.5 mm^2, $p \le 0.021$), taller (mean height 18.6 mm vs. 9.9 mm, $p < 0.001$), more secreting (median PRL ULN_area 23 $\mu g/L/cm^2$ vs. 12.6 $\mu g/L/cm^2$, $p \le 0.032$) and had poorer hormonal response to DA as compared with homogeneous prolactinomas. "Cystic" tumors were diagnosed almost exclusively in women and secreted less prolactin, but showed similar hormonal and tumoral response as "non-cystic" tumors. In homogeneous prolactinomas, the T2-weighted intensity ratio was correlated to prolactin secretion, although not significantly, and did not predict hormonal and tumoral response to DA.

Conclusions Our study confirms that hypo/isointense prolactinoma is a rare finding and suggests for the first time that the heterogeneity of prolactinoma T2 signal at diagnosis might be correlated with a different clinical behavior and could be used as a negative predictor factor of hormonal response to DA.

Keywords Prolactinoma · MRI · Therapy · Dopamine agonists

Introduction

Strong predictive factors for prolactinoma response to dopamine agonists are still lacking although several clinical and radiological characteristics as male sex and cavernous sinus invasiveness are associated with a poorer response to dopamine agonists (DAs) [1]. Recent work supports the use of T2-weighted magnetic resonance imaging (MRI) intensity as a tool for treatment stratification in acromegaly [2]. The T2 signal intensity of somatotroph tumors correlates with the histological subtypes, baseline characteristics, and response to treatment with somatostatin analogs (SSA) [3–5]. T2 hypointense somatotropinomas, whose appearance seems to translate a densely granulated microscopic pattern, are smaller, more secreting and less invasive than more

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intense GH-tumors and they respond better to SSA [4, 6]. Whether the pattern of MRI T2 intensity could be a predictor of hormonal and/or tumoral response to DA in prolactinomas remains unknown.

The objectives of the present study were to characterize the T2-weighted aspect of prolactinomas by measuring the signal of tumoral regions of interest (ROIs) before dopamine agonist (DA) therapy and to correlate the tumor signal intensity and heterogeneity to the prolactin level at diagnosis and to hormonal and tumoral responses after 1 year of DA treatment.

Subjects and methods

We retrospectively reviewed the clinical and radiological data of 422 patients aged over 16 years seen for a putative diagnosis of prolactinoma in one of our two tertiary centers between 2004 and 2016. In order to be included, patients must have a clinical presentation, as well as biochemical and MRI findings clearly suggestive of the diagnosis of prolactinoma. Patients with concomitant medication potentially responsible for hyperprolactinemia were excluded. All patients also had to have been primarily treated with dopamine agonists with both complete baseline and one-year follow-up evaluation performed in our institutions. Patients with clinical apoplexy at first presentation, with elevated IGF1 levels or no available follow-up MRI were excluded. Thus, the final analysis only included 70 patients, 41 with a macroprolactinoma (maximal diameter ≥ 10 mm) and 29 with a clearly defined microprolactinoma (diameter > 5 mm and PRL level at diagnosis > 50 µg/L).

The absolute value of PRL at diagnosis and the superior limit of the normal range adjusted for sex were recorded. In order to eliminate variation caused by different assay kits with different sex-adjusted normal ranges, the PRL levels were expressed as a ratio of the absolute value to the upper limit of the normal range (PRL ULN) and further relative to tumor surface (PRL ULN_area).

Treatment was usually initiated with cabergoline but another dopamine agonist (bromocriptine, quinagolide) was used in eight patients. The doses of dopamine agonists used when prolactin concentration attained its lowest level and at the final evaluation were expressed as equivalent cabergoline doses (Eq CAB dose) (assuming that 5 mg of bromocriptine/day, 75 µg of quinagolide/day and 0.5 mg of cabergoline/week have a roughly similar prolactin-lowering effect). The initial dose of cabergoline was 0.5 mg per week and was increased every 4 to 6 weeks until prolactin normalization. The proportion of tumors with a rapid (≤ 3 months) prolactin normalization ("early prolactin response") was recorded.

The final tumoral and hormonal responses to DA were assessed in 58 prolactinoma patients with available MRI evaluation at 12 months ± 3 months after treatment initiation. MRI evaluation within the first year of DA treatment could not be done in six patients because of pregnancy occurrence and because of early pituitary surgery in two patients. Tumoral response was described as a reduction in tumor surface measured on the coronal gadolinium-enhanced T1 image showing the largest tumoral surface.

MRI studies

Subjects underwent a 3T pituitary MRI (except in two patients where a 1.5 T MRI was performed at diagnosis), with intravenous administration of gadolinium, producing T1-weighted, T2-weighted and gadolinium-enhanced images, at diagnosis and at the time of the tumoral response assessment. All MR images were reviewed by the first author (MCB) and all the measures were done before analyzing the response to the treatment. In case of doubt (evaluation of invasiveness, concurrent non-adenomatous intra or parasellar lesions), the images were also reviewed by the senior neuroradiologist (TD).

Maximal tumor size was defined as maximal diameter on MRI coronal and sagittal planes. The tumor area was measured by outlining the tumor with a cursor on the coronal gadolinium-enhanced T1 image showing the largest tumoral surface. Tumoral invasion, defined as invasion of one or both cavernous sinus, was recorded according to radiological reports and further imaging review in case of doubt.

The PRL tumors were divided into two groups according to their homogeneity on T2 images (homogenous and heterogeneous) (Fig. 1). Heterogenous prolactinomas were defined by the presence in any of the MRI slices of at least one area of more than 5 mm (or more than 30% of the maximal coronal surface for microprolactinomas) appearing brighter (more intense) or darker (less intense) than the rest of the tumor.

In all tumors, T2 signal intensity was measured by outlining the whole tumor on the coronal T2-weighted image showing the largest tumoral surface. One circular ROI was also drawn in a standardized area of temporal gray matter (amygdala) and was used as reference to establish a "T2 intensity ratio" (tumor/gray matter) (Fig. 2). PRL tumors with T2 intensity ratio lower than or equal to 1.0 were arbitrarily classified as hypo/isointense and tumors with an intensity ratio > 1.0 as hyperintense.

We also separately analyzed a subgroup of prolactinomas, which were visually very bright ("cystic"-like) in more than 50% of the surface measured on the coronal T2 image showing the largest tumoral area. "Cystic" T2 intensity was further confirmed by a ratio between intensity of the tumoral

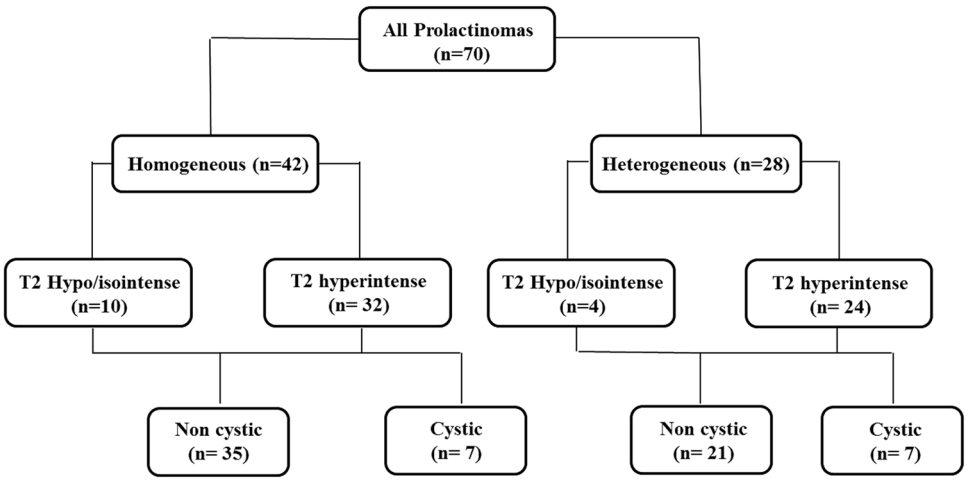

Fig. 1 Distribution of prolactinomas according to their T2-weighted aspects on magnetic resonance imaging (heterogeneity, intensity, and cystic feature). For definition of these characteristics, see material and methods

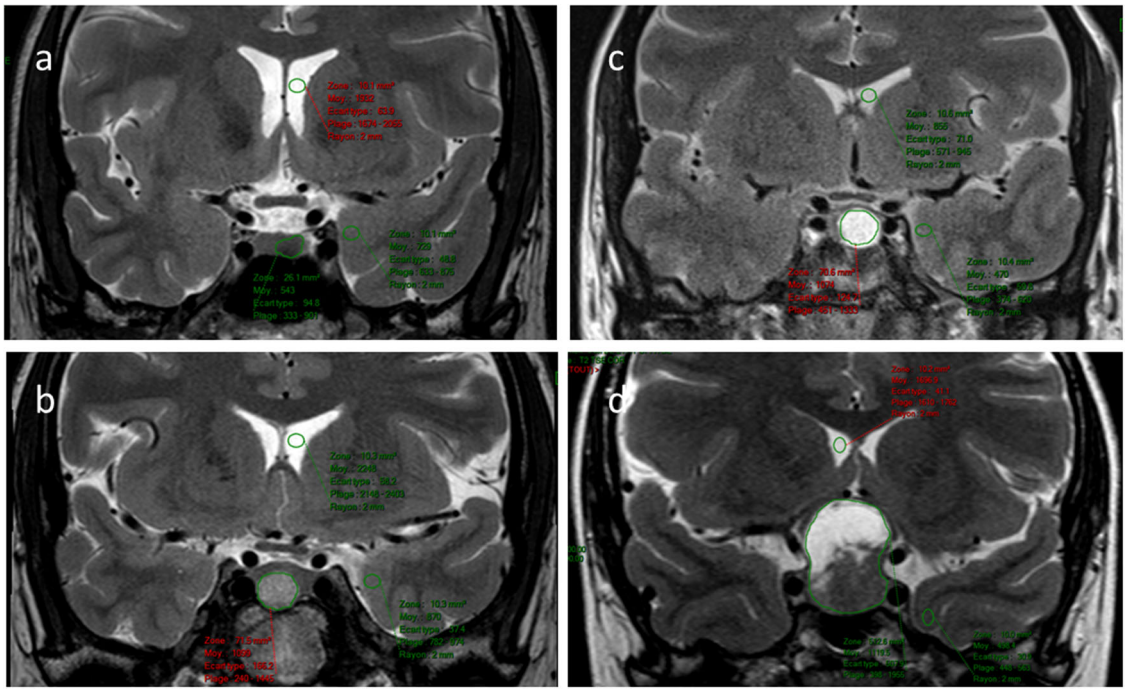

Fig. 2 MRI coronal sections performed in three patients with a homogeneous prolactinoma and one with a heterogeneous prolactinoma. Depicted regions of interest (ROI) in the adenoma (arrow), gray matter (arrow), and CSF fluid (arrow). **a** Homogeneous hypointense tumor with a T2 intensity ratio of 0.74; **b** Homogeneous hyperintense "non-cystic" tumor with a T2 intensity ratio of 1.26; **c** Homogeneous hyperintense "cystic" tumor with a T2 intensity ratio of 2.28; **d** Heterogeneous "cystic" tumor with a T2 intensity ratio of 2.24

region of interest and CSF intensity equal to or more than 1. Prolactinomas presenting with this aspect will be further referred as "cystic" prolactinomas, independent of the precise nature of their content (Figs. 1 and 2).

Statistical analyses

The SSPPS version 23.0 was used for statistical analyses. Data are presented as mean ± standard deviation (SD) if normally distributed, or as median and [P5-P95] range if not normally distributed. Continuous data were compared using independent Student *t*-tests or by ANOVA followed by Student-Newman-Keul's tests, while categorical variables were compared by Chi-square analysis. Statistics were performed after log transformation of prolactin concentrations. Logistic regression analyses (both uni- and multivariate) were also performed to analyze factors predicting a good response to DA. This good response was arbitrarily defined as both normalization of prolactin concentrations and a more than 50%-reduction of the largest tumor coronal surface after 1 year of medical treatment. Only variables that showed some significance in the univariate analysis (*p*

< 0.100) were introduced into the multivariate model. Two sided p-values were deemed significant at $p < 0.05$.

Results

Patient characteristics

Seventy patients (25 men and 45 women; 29 microadenomas and 41 macroadenomas) met our strict inclusion criteria. The mean age at diagnosis of prolactinoma was younger in women (29.7 ± 8.1 vs. 46.0 ± 15.9 years in men, $p < 0.001$). Prolactinomas in men were larger (mean tumor area 4.5 cm^2 vs. 1.1 cm^2 in women, $p < 0.001$), more secreting (PRL ULN_area 24.7 [4.5–73.9 µg/L/cm^2] vs. 9.6 [3.0–38.5 µg/L/cm^2], $p < 0.001$) and more often invasive (12/25 men vs. 3/45 women, $p < 0.001$).There were significantly more microadenomas in women than in men (57% vs. 12%, $p < 0.001$).

The mean T2 intensity ratio at diagnosis in the whole study population was 1.4 ± 0.6. Fifty-six prolactinomas (80%) had a T2 intensity ratio > 1.0 and were thus categorized as hyperintense (Fig. 1). T2 intensity ratio was lower in men than in women but this difference was not statistically significant (1.4 ± 0.4 vs. 1.5 ± 0.6, $p = 0.126$).

Tumor MRI characteristics and response to treatment

Hypo/isointense vs. hyperintense tumors

There was no difference between hypo/isointense and hyperintense prolactinomas in terms of age, sex ratio, tumor characteristics, and PRL secretion at diagnosis (Table 1). Tumoral and PRL response to DA treatment could be assessed in 13 (93%) of the hypo/isointense and 45 (80%) of the hyperintense prolactinomas. Their baseline general characteristics were similar and there were no differences in tumoral or hormonal response at 1 year (Online resource 1). Likewise, there was no difference in PRL secretion (whether in absolute values or per unit of surface) between hypo/isointense and hyperintense homogeneous groups (PRL ULN 4.3 [1.4–26.9] µg/L vs. 6.8 [1.6–281.8] µg/L, $p = 0.342$; PRL ULN_area 13.6 [3.8–35.7] µg/L/cm^2 vs. 12.1 [2.8–39.1] µg/L/cm^2, $p = 0.679$). However, in homogeneous tumors, the T2-weighted intensity ratio was inversely correlated to prolactin secretion, although not reaching statistical significance ($r = 0.302$; $p = 0.052$) (Fig. 3).

When only homogenous non-cystic prolactinomas were considered ($n = 35$), similar observations were made. In particular, there was no difference in the response to treatment between T2 hypo/isointense ($n = 10$) and T2 hyperintense tumors (data not shown) and a relationship between baseline T2 intensity and prolactin secretion was further confirmed. Indeed, homogeneous non-cystic hypo/isointense prolactinomas secreted more prolactin per unit of tumor surface than homogeneous non-cystic hyperintense tumors (log PRL ULN_Area at diagnosis (µg/L/cm^2) 4.8 [3.2–11.3] vs. 3.3 [0.2–8.1], $p = 0.03$).

Table 1 General characteristics in patients with hypo/isointense ($n = 14$) and hyperintense ($n = 56$) prolactinomas

	Hypo/isointense ($n = 14$)	Hyperintense ($n = 56$)	p-value
Age at diagnosis (years)	35.4 ± 11.3	35.4 ± 14.4	0.990
Sex ratio (M/F)	5/9	20/36	1.000
% Macroadenomas	5/14 (35.7%)	36/56 (64.3%)	0.052
% Invasive tumors	2/14 (14.3%)	13/56 (23.2%)	0.466
Tumor height (mm)	9.8 ± 8.0	14.62 ± 10.5	0.157
Tumor surface (mm^2)	55.0 [17.0–51.5]	94.0 [19.1–1157.2]	0.212
T2 intensity ratio	0.87 ± 0.10	1.61 ± 0.54	<0.001
PRL at diagnosis (µg/L)	152.5 [47.0–1529.0]	233.7 [49.7–6855.7]	0.126[a]
PRL at diagnosis (xULN)	7.6 [1.38–127.4]	11.9 [1.8–512.1]	0.290[a]
PRL ULN_area at diagnosis (µg/L/cm^2)	13.6 [3.7–34.9]	13.3 [3.1–47.1]	0.631[a]

Values are shown as means ± standard deviations, medians, and [P5-P95] intervals or proportions

PRL prolactin, *ULN* upper normal limit

[a]Statistics performed after log transformation of prolactin concentrations

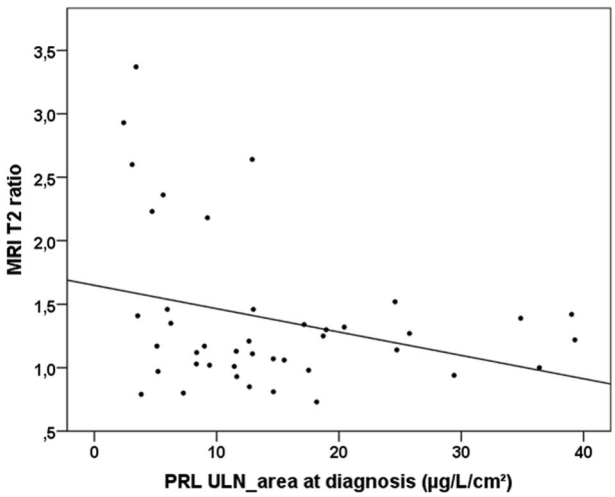

Fig. 3 Correlation between T2 intensity ratio of the pituitary PRL-secreting tumor and baseline PRL secretion in the group of homogeneous prolactinomas ($r = 0.302$; $p = 0.052$)

Heterogeneous vs. homogeneous tumors

Heterogeneous tumors represented 28/70 (40%) of all prolactinomas (Fig. 1) and most of them (24 patients, 86%) were macroadenomas (Table 2). They were diagnosed at an

age similar to that of patients with homogeneous tumors. Heterogeneous prolactinomas were significantly larger and more secreting than homogeneous prolactinomas and they had more cranial growth than the homogeneous prolactinomas ($p < 0.001$) but there was no significant difference in the propensity for invasiveness between both subgroups ($p = 0.234$) (Table 2). Women had more often homogeneous prolactinomas than men (71.1% vs. 40.0%, $p = 0.011$).

Table 2 General characteristics in patients with homogeneous ($n = 42$) and heterogeneous ($n = 28$) prolactinomas

	Homogenous ($n = 42$)	Heterogenous ($n = 28$)	p-value
Age at diagnosis (years)	35.2 ± 12.3	35.9 ± 16.0	0.832
Sex ratio (M/F)	10/32	15/13	0.011
% Hypo/isointense	10/42 (23,8%)	4/28 (14,3%)	0.329
% "Cystic" tumors	7/42 (16.7%)	7/28 (25.0%)	0.393
% Macroadenomas	17/42 (40.5%)	24/28 (85.7%)	<0.001
% Invasive tumors	7/42 (16.7%)	8/28 (28.6%)	0.234
Tumor height (mm)	9.9 ± 8.4	18.6 ± 10.6	<0.001
Tumor surface (mm²)	56.5 [17.5–1001.9]	304.5 [28.9–1275.3]	0.021
T2 intensity ratio	1.38 ± 0.61	1.60 ± 0.49	0.126
PRL at diagnosis (µg/L)	160.2 [47.2–2549.6]	767.5 [85.7–10786.5]	<0.001[a]
PRL at diagnosis (xULN)	5.9 [1.5–158.1]	43.9 [4.1–768.9]	<0.001[a]
PRL ULN_Area at diagnosis (µg/L/cm²)	12.6 [3.1–38.6]	23.0 [3.4–68.5]	0.032[a]

Values are shown as means ± standard deviations, medians, and [P5-P95] intervals or proportions

PRL prolactin, *ULN* upper normal limit

[a]Statistics performed after log transformation of prolactin concentrations

Tumoral and PRL response after 1 year of DA treatment could be assessed in 33 (78%) of the homogeneous and 25 (89%) of the heterogeneous prolactinomas. The differences in baseline general characteristics between these two subgroups were similar to those observed when all homogeneous and heterogeneous tumors were compared. Early hormonal response tended to be more frequent in homogeneous tumors and the PRL nadir was attained at a lower dose of dopamine agonist in the homogeneous group (0.90 ± 0.46 vs. 1.21 ± 0.63 mg/week, $p = 0.038$) (Table 3). After 1 year of medical treatment, prolactin was normalized in 28/33 (84.8%) homogeneous vs. only 15/25 (60.0%) heterogeneous prolactinomas ($p = 0.032$) (Table 3). Only three (7%) of the homogeneous compared to six (21%) of the heterogeneous prolactinomas needed at least 2 mg/week (max 3.5 mg/week) of cabergoline to reach the PRL nadir.

There was no difference in tumoral response between the two groups at 1 year radiological evaluation. At this time, only one homogeneous vs. three heterogeneous prolactinomas were still receiving more than 2 mg cabergoline (max 3.5 mg) and the dopamine agonist dose was no longer different between groups. All heterogeneous prolactinomas were receiving cabergoline vs. only 75.8 % of homogeneous tumors (21.2% were on quinagolide and 1 patient (3%) took bromocriptine; $p = 0.034$). Similar baseline characteristics and response to treatment were noted when considering only non-cystic prolactinomas ($n = 56$) (data not shown).

Ten prolactinoma patients (five homogeneous and five heterogeneous, 14% of prolactinomas) had pituitary surgery during long-term follow-up. The reasons for pituitary surgery for the five heterogeneous prolactinomas were clinical apoplexy in three patients and tumor progression in two, with compression signs in one. Of the five homogeneous prolactinomas, only one was referred for apoplexy 1 month after cabergoline initiation, one for tumor progression and in the other three, despite tumoral response, surgery was

Table 3 Response to dopamine agonists in patients with homogeneous ($n = 33$) and heterogeneous ($n = 25$) prolactinomas evaluated by MRI after 1 year of DA treatment

	Homogenous ($n = 33$)	Heterogenous ($n = 25$)	p-value
CAB dose (mg/week)	0.90 ± 0.46	1.21 ± 0.63	0.038
CAB dose at 1 year (mg/week)	0.80 ± 0.44	0.97 ± 0.64	0.226
Time to MRI evaluation (months)	11.6 ± 1.8	12.1 ± 1.9	0.369
% With early PRL control	23/29 (79.3%)	14/24 (58.3%)	0.098
PRL value at 1 year (µg/L)	9.9 [0.3–136.2]	9.7 [0.6–236.8]	0.366[a]
% With normal PRL at 1 year	28/33 (84.8%)	15/25 (60.0%)	0.032
Tumor surface at 1 year (mm²)	36.0 [3.5–366.8]	141.0 [15.6–488.0]	0.003
Surface decrease at 1 year (%)	−50.0 [−24.9 −84.1]	−51.9 [−127.4 −89.0]	0.637
% With tumor surface reduction > 50%	17/33 (51.5%)	13/25 (52.0%)	0.971

Values are shown as means ± standard deviations, medians, and [P5-P95] intervals or proportions

CAB dose cabergoline dose at first PRL normalization, *PRL* prolactin, *DA* dopamine agonist

[a]Statistics performed after log transformation of prolactin concentrations

Table 4 General characteristics in patients with « cystic » ($n = 14$) and « non-cystic » ($n = 56$) prolactinomas

	Cystic ($n = 14$)	Non-cystic ($n = 56$)	p-value
Age at diagnosis (years)	26.2 ± 8.6	37.7 ± 14.0	0.004
Sex ratio (M/F)	1/13	24/32	0.013
% Homogeneous	7/14 (50%)	37/56 (66%)	0.266
% Macroadenomas	8/14 (57%)	33/56 (59%)	0.903
% Invasive tumors	0/14 (0%)	15/56 (27%)	0.029
Tumor height (mm)	13.1 ± 8.0	13.4 ± 11.0	0.934
Tumor surface (cm²)	1.1 [0.1–4.9]	0.8 [0.2–11.5]	0.529
T2 intensity ratio	2.3 ± 0.5	1.2 ± 0.3	<0.001
PRL at diagnosis (µg/L)	164.0 [35.0–1272.5]	220.0 [54.8–6855.7]	0.138[a]
PRL at diagnosis (xULN)	7.7 [1.4–62.8]	11.1 [1.8–512.1]	0.083[a]
PRL ULN_Area at diagnosis (µg/L/cm²)	8.0 [2.4–14.2]	16.6 [3.8–47.1]	<0.001[a]

Values are shown as means ± standard deviations, medians, and [P5-P95] intervals or proportions

PRL prolactin, *ULN* upper normal limit

[a]Statistics performed after log transformation of prolactin concentrations

elected because of cabergoline intolerance (one patient) or patient's preference (two patients). There was thus a tendency for a more frequent need for surgery due to apoplexy or tumor progression in the group of heterogeneous prolactinomas ($p = 0.074$)

When analyzing factors that could predict a good response to DA (defined as both normalization of prolactin concentrations and a more than 50%-reduction of the largest tumor coronal surface after 1 year of medical treatment), male gender, tumor height, and T2 signal heterogeneity nearly and similarly reached a significance level in univariate analysis (p-values between 0.061 and 0.067), while invasiveness and T2 signal intensity were not significantly associated with responsiveness to DA in our study (Online resource 2). However, none of these factors emerged as more significant in multivariate analysis (p-values between 0.291 and 0.434), likely due to the low number of subjects.

When considering only the non-cystic prolactinomas, T2 signal heterogeneity was the only factor reaching a significance level in univariate analysis ($p = 0.050$, Online resource 3).

"Cystic" vs. "non-cystic" tumors

"Cystic" prolactinomas represented 20% (14/70) of all tumors (Fig. 1) and were almost exclusively diagnosed in women (13 women vs. one man, $p = 0.013$). Half of them were homogeneous and the other half heterogeneous (including the only man). "Cystic" tumors developed in younger patients and none was invasive ($p = 0.029$) (Table 4). All "cystic" prolactinomas had a T2 intensity ratio > 1 and 10/14 (71%) of them a T2 ratio > 2. Of note, visually selected "cystic" prolactinomas were correctly classified as more intense than" non-cystic" prolactinomas when T2 intensity measure was performed (T2 intensity ratio 2.3 ± 0.5 vs. 1.2 ± 0.3, $p < 0.001$) (Table 4).

"Cystic" prolactinomas were clearly less secreting than their "non-cystic" counterparts although the size of adenomas of the two groups was similar (Table 4). The same observation was made within the homogeneous and the heterogeneous groups (Homogeneous group: PRL ULN_area at diagnosis 4.7[2.4–9.2] µg/L/cm² in "cystic" vs. 13.0[4.0–39.2] µg/L/cm² in hyperintense vs. 13.6 [3.8–35.7] µg/L/cm² in hypo/isointense, $p = 0.041$; Heterogeneous group: PRL ULN_area at diagnosis 10.0 [3.1–81.2] µg/L/cm² in "cystic" vs. 24.4 [3.8–81.2] µg/L/cm² in "non-cystic", $p = 0.028$).

The PRL and tumoral response after 1 year of DA treatment was evaluated in twelve "cystic" and forty-six "non-cystic" prolactinomas. There was no significant difference between these two groups in term of amplitude and rapidity of the prolactin or tumoral response or in term of medical treatment, but the "cystic" tumors were evaluated slightly earlier (data not shown).

Five out of 14 (36%) "cystic" prolactinomas were referred for surgery. All but one of these patients had heterogeneous tumors.

Discussion

By using a quantitative, operator unbiased method, our study shows that more than three-quarters (80%) of the prolactinomas are hyperintense on T2-weighted MRI sequences when the normal gray matter of the same patient is used as the reference tissue. This figure is close to that found in the study of Kreutz et al. [7] where 47 out of 74 prolactinomas (63%) where visually classified as hyperintense, after exclusion of hemorrhagic tumors. In another study that used both the white and the gray matter as a visual comparator for the solid portion of the adenoma, 62% of prolactinomas were found hyperintense, 36% isointense and 2% hypointense [3]. Even when selecting a subgroup of 42 homogeneous prolactinomas, we confirmed the predominance of hyperintense tumors as only 10/42 (24%) were hypo/isointense. However, we could not confirm in our study a gender difference of prolactinomas T2 intensity as reported in a previous study that included only a few female macroadenomas and exclusively non-hemorrhagic tumors [7].

The choice of the reference tissue is essential in order to standardize results of T2 intensity measurements across different centers and studies. In acromegaly, quantitatively assessed T2 intensity ratio between adenoma and gray matter of the right amygdala correlates with visual assessment [4, 6]. The use of the gray matter as a comparator was suggested because it has very similar signal intensity to that of the normal pituitary tissue [2] and, at the difference of non-adenomatous pituitary, normal brain is rarely compromised by any displacement due to tumor extension [5]. Moreover, the use of the T2 ratio largely corrects for signal variations between patients and for differences in image acquisition time points and MRI technical specificities.

While most of the prolactinomas are hyperintense, most of somatotropinomas are hypointense on T2-weighted images. The molecular characteristics behind the different appearances of adenomas are not completely understood but granulation pattern has been correlated with T2 intensity and response to the medical treatment in acromegaly [3]. Densely granulated GH-adenomas tend to exhibit lower T2 signal than sparsely granulated tumors [8] and the latter pattern was associated with larger adenomas and resistance to somatostatin analogs treatment [3, 9]. Densely granulated pattern is a very rare finding in prolactinomas [10]. All the 132 prolactinomas identified during a large postmortem study of 3048 pituitaries were classified as sparsely granulated [11]. Accordingly, in a surgical series of 40 prolactinomas including hemorrhagic and cystic adenomas, all tumors proved to be sparsely granulated at histological examination [12]. In the study by Hagiwara et al. [3]., granulation pattern of the only hypointense prolactinoma could not be assessed. It should be noted, however, that in our series, all resected hypo/isointense and hyperintense prolactinomas were classified histologically as chromophobe tumors with juxtanuclear immunoreactivity for PRL, a feature of sparsely granulated adenoma.

Moreover, at the difference of somatotropinomas, we did not find a significant correlation between the prolactinoma T2-weighted intensity at MRI and the amount of PRL secretion, although a similar trend was noted, less intense adenoma being more secreting. The hormonal and tumoral response of prolactinomas to medical treatment was similar between T2 intensity groups in our series. However, given the relatively small number of patients, further studies regarding the relationship between prolactinomas granulation pattern, hormonal secretion, and T2 intensity category are needed.

Pituitary neuroendocrine tumors can exhibit degenerative features such as fibrosis, calcification, hyaline accumulation, necrosis and focal hemorrhage leading to heterogeneity. The latter changes are common in large prolactinomas, particularly in the sparsely granulated type [13, 14]. In a recent clinical study, pituitary hemorrhage assessed by radiological criteria was found in about 7% of 368 prolactinomas, mostly in macroadenomas, and the vast majority of them were clinically silent [15]. The prevalence of pituitary hemorrhage in surgical series goes up to 18% when macroadenomas predominate and both clinical and subclinical states of apoplexy are considered [16].

At the difference of previous studies that analyzed only [17] the solid portion of prolactinomas for T2 intensity classification and excluded hemorrhagic tumors [3, 7], our study included all types of prolactinomas, including those with radiological changes suggestive of partial hemorrhagic, cystic or necrotic transformation. We presume that these changes were the rule in the heterogeneous group, but we cannot exclude other causes of heterogeneity as only 14% of prolactinomas had a histological diagnosis. It has been reported that pituitary apoplexy occurs more frequently in tumors with predominant cranial growth, thus compressing the superior hypophyseal artery as a possible pathological mechanism [18]. We indeed found that heterogeneous prolactinomas were taller than homogeneous tumors and that, when surgery was needed, heterogeneous tumors were operated in all cases for clinical apoplexy or tumoral symptoms.

In contrast to other previous studies on the same issue, we choose to analyze the whole tumor because (i) at the difference of other pituitary adenomas, we believe that heterogeneity is an important characteristic of prolactinomas; (ii) when evaluating the response to medical treatment, the whole tumor should be considered and not only the solid component; (iii) we also believe it is an easier and more accurate tool for the radiologist and the clinician to delineate the whole tumor, as cystic parts may be disseminated within the pituitary mass. Moreover, we did not observed differences in baseline characteristics and response to treatment when all prolactinomas or only those without gross heterogeneity were considered.

An important finding of our study is that heterogeneous prolactinomas are more frequent in men, are larger, secrete more PRL, need larger doses of DA to normalize PRL level and might be more prone to progression or clinical apoplexy. Predominance of larger, often invasive and frequently cabergoline resistant prolactinomas in men is well established and was attributed to a faster growing potential with male prolactinomas exhibiting higher indexes of proliferating cells by Ki-67 immunoreactivity [19]. In acromegaly patients treated with SSA, high homogeneity of tumor signal intensity was associated with a blunted tumoral response ($r = 0.40$, $p = 0.034$) [5]. In contrast, in our prolactinoma series, homogeneous tumors were associated with a better PRL response and a similar tumoral response to dopamine agonists. Moreover, MRI T2 signal heterogeneity appeared to be a factor as strong as gender and tumor height to predict poor global response to DA, without clear

interdependence between these variables in multivariate analysis. These findings point out the heterogeneity of pituitary tumors as a potential marker for response to medical treatment, although its significance may be opposite in different tumor types.

Our study also addressed the characteristics of the T2 very hyperintense tumors, which are suggestive of cystic lesions. In a large series of hyperprolactinemia patients, 77 out of 139 (55%) sellar cystic lesions were classified as cystic prolactinomas [20]. In their final analysis, cystic prolactinomas were overrepresented in women (24/30) and had a median baseline prolactin value of 106 ng/mL for a median cyst volume of 435 mm^3. In our qualitatively assessed heterogeneity prolactinoma population, "cystic" prolactinomas represented 20% of the tumors, all but one were diagnosed in women and all were significantly less secreting than non-"cystic" tumors. Moreover, we showed that "cystic" tumors, that we believe correspond mostly to cystic prolactinomas, had similar hormonal and tumoral response to their non-"cystic" counterparts. In the literature, it was only recently recognized that medical therapy may be as effective in cystic prolactinomas as in non-cystic ones [20].

Limitations of our study include a low number of analyzed patients and the facts that we did not have a pathological traduction of T2 intensity characteristics in all patients and we did not use the T1-weighted sequences for the differential diagnosis of T2 hyperintense lesions. A bright, hyperintense T2 signal was described in hemorrhagic adenomas and intratumoral cysts resulting from hemorrhage transformation but also in Rathke's cleft cysts, craniopharyngiomas, arachnoid cysts and other non-PRL-secreting cystic adenomas. As our study intended to offer to the endocrinologists a prognostic tool easy to use when the prolactinoma patient is first addressed, we did not wish to burden the radiological evaluation. Nevertheless, the carefully selected clinical and biological inclusion criteria of the patients as well as the overwhelming response to the DA in this population validate our series of prolactinomas. Another limitation, which also holds true for previous similar studies reported in the literature, is the observational retrospective non-controlled nature of our findings that need further confirmation in larger prospective studies.

In conclusion, our study confirms that MRI T2-weighted hypo/isointensity is a rare finding in prolactinomas and shows that T2-weighed signal heterogeneity is a common feature of macroprolactinomas. T2 heterogeneity rather than T2 intensity of prolactin secreting adenoma correlates with the clinical behavior under DA. Using an easy-to-use quantification of both T2 signal intensity and homogeneity, we suggest for the first time that the T2 heterogeneity of prolactinoma at diagnosis might be used as a potential new predictive factor of poorer hormonal response to DA. Indeed, although heterogeneous prolactinomas may exhibit similar regressive tumoral changes as homogeneous tumors, they should probably be managed more carefully because of a lower sensitivity to dopamine agonists and possibly a higher risk of apoplexy or progression.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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