

Intensity of prolactinoma on T2-weighted magnetic resonance imaging: towards another gender difference

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Abstract

Introduction Clinical presentations of prolactinomas are quite different between genders. In comparison with women's prolactinoma, those in men showed predominance of large tumors with high prolactin (PRL) levels. This preponderance could be attributed to a greater proliferative potential of the tumors.

Differences in magnetic resonance imaging (MRI) signal at diagnosis have not been yet clearly evaluated.

Methods We conduct a retrospective study comparing MRI signal intensity (SI) on T2-weighted images (T2-WI) between 41 men and 41 women to investigate whether or not men prolactinoma present specific features.

Results In addition to the size of the adenoma and PRL levels ($P < 0001$), prolactinomas in men also exhibit differences from those in women in signal on T2-WI on MRI ($P < 0001$). Women's prolactinomas are mostly of high SI on T2-WI while men's prolactinomas exhibit a more heterogeneous pattern of SI on T2-WI. Prolactinomas presenting with low SI on T2-WI are almost exclusively encountered in men.

Conclusions Presence of T2-WI hypointensities in pituitary adenoma can be predictive of a different subtype of prolactinoma almost encountered in men and possibly translate the presence of spherical amyloid deposits, in agreement with the literature.

Keywords Prolactinoma · Men · Calcifications · Magnetic resonance imaging

Introduction

The prevalence of clinically significant pituitary adenomas has been reported in 2006 of approximately 1 case per thousand of the population (1:1064) [1]. Although their proportion can range from 40 to 66 % across various studies, prolactinomas are the most prevalent subtype of pituitary tumors [1–3]. Prolactinomas affect more women with a sex ratio of 10:1 between eighteen years old and the fifth decade. This discrepancy disappears after 50 years of age, when the ratio returns 1:1 [4, 5].

At the time of diagnosis, men with prolactinomas showed frequently predominance of large tumors with high PRL levels [6, 7]. This preponderance has been attributed to a longer delay in diagnosis. However, predominance of larger prolactinomas in men, often invasive and cabergoline resistant, has also been attributed to a greater proliferative potential of the tumor [8]. Because of these gender-related differences at presentation, we conduct a retrospective study comparing MRI SI on T2-WI to investigate whether or not men prolactinomas present specific features.

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Patients and methods

Patients

We retrospectively reviewed the clinical and radiological features of all men (41) diagnosed with prolactinoma between 2003 and 2014 in two medical tertiary centers. For comparison, we reviewed 41 women diagnosed of prolactinoma between the same period of time randomly selected.

Endocrinological examination, including thyrotropin test, was performed in all patients. Patients taking drugs known to affect serum prolactin levels were excluded as well as non-tumoral hyperprolactinemia.

Imaging and analysis

All patients underwent MR imaging with a 1.5 or a 3.0-T whole-body system (respectively, Aera and Trio; Siemens Healthcare, Germany) or a 3.0-T whole-body system (Excite; GE Healthcare) with a standard head coil.

MR imaging included coronal turbo spin-echo T2-weighted sequence (TR/TE, respectively, Aera and Trio 4000/130 and 3000/125 msec, FOV 21 cm, matrix 384×384, 2-mm section thickness) or coronal fast spin echo T2-weighted sequence (Excite TR/TE 3500/140 msec, FOV 20 cm, matrix 384×384, 2-mm section thickness), sagittal spin-echo T1-weighted sequence (TR/TE, respectively, Aera and Trio 400/9 and 450/9 msec, FOV 21 cm, matrix 384×384, 3-mm section thickness) or sagittal FLAIR T1-weighted sequence (Excite, TR /TE/TI 2500/6.5/920 msec, FOV 26 cm, matrix 384×256, 2.5-mm section thickness) nonenhanced sequences. Coronal spin-echo T1-weighted sequences (TR/TE, respectively Aera and Trio 450/9 and 500/9 msec, FOV 21 cm, matrix 384×384, 3-mm section thickness; or Excite TR/TE 700/14 msec, FOV 23 cm, matrix 416×256, 3-mm section thickness) were performed after IV administration of 0.1 mmol per kilogram of gadodiamide (Dotarem, Caudalie).

All tumor diameters were estimated by coronal and sagittal sections, and the maximal tumor diameter was considered. All image analysis was performed by two neuroradiologists with certificate of added qualification (J.B., F.C.). Careful visual analysis of the signal intensity (SI) on T2-WI of solid-appearing portions determine three grades of SI (hypointensity, isointensity, hyperintensity) of the adenoma in comparison with the SI of the normal grey matter in the same patient. Hemorrhagic areas (unenhanced T1-weighted hyperintensity, T2-weighted hypointensity) were intentionally excluded.

Data of available cerebral CT (Somatom sensation 16; Siemens Healthcare, Germany or Brilliance 64; Philips Healthcare Netherlands) were evaluated. The parameters were respectively for Somatom and Brilliance as follows: FOV 22.5 cm, tube current 300 mAs, tube voltage 120 kV, 5-mm section thickness; FOV 16 cm, tube current 351 mAs, tube

voltage 120 kV, 5-mm section thickness. Region of interest (ROIs) for density (U.H.) were drawn directly on the images obtained. All ROIs were chosen of uniform shape and size (elliptic 10 mm²), in the portion of adenoma presenting visual high-density spots if present or in the central portions of the adenoma.

Statistical analysis

Data are presented as median (first, third quartile). The non-parametric Wilcoxon two-sample rank sum test was used to compare the geometric means of the study groups. The frequency of observations between men and women was compared by χ^2 test and Fischer's exact probability where appropriate. The level of significance was set at $P < 0.001$.

Results

Baseline clinical characteristics in men and women are summarized in Table 1.

The median age at diagnosis was 44 years [35, 54] in men and 29 years [25, 38] in women ($P < 0.001$).

The median pretreatment serum PRL level was significantly higher in men 666 [250, 2607] ng/ml than in women 109 [65, 142] ng/ml ($P < 0.001$).

The maximal tumor diameter in men and women ranged from 6 to 50 (20 [16, 25]) mm in men and from 5 to 13 (8 [6,

Table 1 Summary of findings in women and men with prolactinomas

	Women	Men	<i>P</i>
Total number	41	41	
Median age (years)	29 [25; 38]	44 [35; 54]	<0.001
Basal prolactin levels (ng/ml)	109 [65; 142]	666 [250; 2607]	<0.001
Maximal tumor diameter (mm)	8 [6; 10]	20 [16; 25]	<0.001
Macroadenoma (%)	10 (24 %)	33 (80 %)	<0.001
Prolactinomas with on T2 ¹	<i>n</i> =35	<i>n</i> =39	<0.001
HSI	32 (91 %)	15 (39 %)	
LSI	1 (3 %)	6 (15 %)	
ISI	2 (6 %)	18 (46 %)	
CSI (%)	1 (10 %)	13 (39 %)	NS
Optic chiasm compression (%)	2 (20 %)	11 (33 %)	NS

Values are expressed as median (first, third quartile). CSI and optic chiasm compression was considered between macroadenoma only. Value was considered statistically significant $P < 0.001$

T2 T2-weighted image, HSI high signal intensity, LSI low signal intensity, ISI isosignal intensity in comparison with grey matter, CSI cavernous sinus invasion

¹ Because of hemorrhagic component, six women and two men were excluded for the analysis of T2-weighted intensity

10] mm in women. Prolactinomas were significantly larger in men than in women.

Although not statistically significant, macroadenomas invade more frequently cavernous sinus in men (13 of 33) than in women (1 of 10) and optic chiasm compression was more frequently encountered in men (11 of 33) than in women (2 of 10).

In addition to the size of the adenoma and PRL levels, prolactinomas in men also exhibit differences from those in women in signal on MRI. Prolactinomas with apparent intratumoral hemorrhage (indicated by high SI on T1- and low SI on T2-WI) were excluded for signal analysis on T2-WI (6 women, 2 men). According to T2-WI signal characteristics between both sex at diagnosis, prolactinomas in women are mostly adenoma of high SI (91 %) with only 6 % of formation of iso SI and 3 % of adenoma of low SI, while men prolactinomas represent a more heterogeneous group with formation of high SI (39 %), iso SI (46 %), and low SI (15 %) ($P < 0001$).

Nine out of 41 men underwent a cerebral CT. Four of them presented very high-density granular spots within the sella. Value of these high densities varies between 119 and 893 HU. Corresponding T2-WI revealed iso (one patient) to hyposignal spots (three patients), the lesser signal corresponding to the higher density on CT (Fig. 1). Table 2 summarizes radiological and clinical features of these four cases illustrated in Fig. 1. All those “pseudo-calcified” prolactinomas were macroadenomas and none of them presented with invasion of cavernous sinus. Five women underwent a CT at the time of diagnosis. None of them present high-density spots on CT.

Discussion

Gender-related differences in prolactinomas are well known. Prolactinomas are relatively rare in men in comparison with

women. Men prolactinomas are usually large and invasive tumors with quite high serum prolactin levels at the time of diagnosis [6]. Young women quickly notice clinically evident signs, which included amenorrhea, galactorrhea, infertility, and libido loss. In men and in postmenopausal women, the endocrinological complains are less frequent and the adenoma is most frequently revealed by tumoral mass effects (headache, visual field impairment) or discovered by chance.

Predominance of larger prolactinomas in men, often invasive and frequently cabergoline resistant, can be a consequence of faster growing tumors, suggesting a particular genetic pattern. Delgrange et al. concluded that the predominance of large prolactinomas in men is due to a high frequency of rapidly growing tumors as macroprolactinomas in males exhibited higher indexes of proliferating cells by Ki-67 immunoreactivity than did similar tumors in female patients [8]. Genetic predisposition to prolactinomas, represented by MEN1 disease, FIPA and AIP mutations in sporadic patients, appeared as a risk factor to develop pharmacological resistance [9]. Raverot et al. identified clinical and histological factors that relate to prolactin tumor recurrence or progression. In the same study, they also identified seven genes associated with tumor recurrence or progression [10].

To our knowledge, our study is the first to demonstrate a statistical significant difference between men and women prolactinomas in signal intensities on T2-WI at the time of diagnosis. Prolactinomas in women are mostly revealed as lesion of high SI on T2-WI (91 %). In men, prolactinomas present with more various pattern of signal on T2-WI. Interestingly, 15 % of men prolactinomas present with low intensity on T2-WI, a result rarely reported in literature. Moreover, in our study, low intensity on T2-

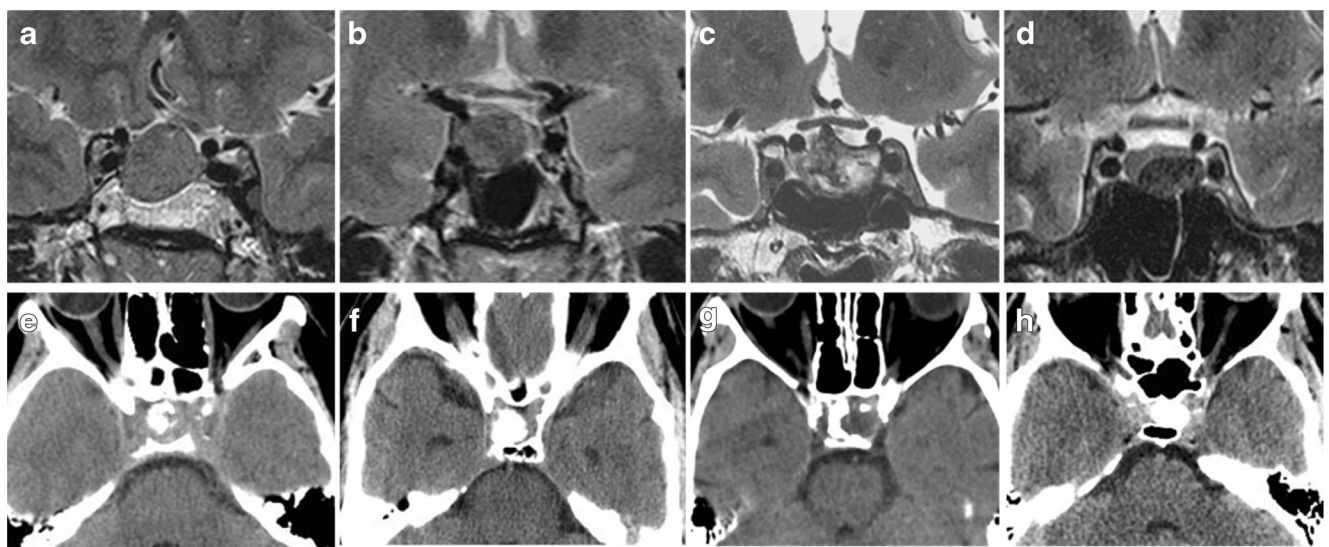


Fig. 1 Coronal T2-WI and axial CT of, respectively, case 1 (a, e), case 2 (b, f), case 3 (c, g), and case 4 (d, h) of Table 2

Table 2 Summary of findings in men prolactinomas presenting with high density spots on CT

Case	Age at diagnosis (years)	UH	T1-WI	T2-WI	Tumor maximal diameter (mm)	CSI	PRL (ng/ml)
1	34	119	Hypo	Iso, partially hypo	18	0	1159
2	43	250	Hypo	Hypo	16	0	280
3	46	504	Hypo	Partially hypo	18	0	377
4	36	893	hypo	Hypo ++	17	0	312

Hypo, Iso: respectively hyposignal and isosignal in comparison with normal pituitary or with grey matter of the temporal lobe

CSI cavernous sinus invasion, T1-WI and T2-WI T1 and T2 weighted image

WI seems to correspond to high-density spots on CT (four cases).

Low signal intensity on T2-WI can be seen with other sellar and parasellar masses.

Craniopharyngiomas, meningiomas, chordomas, teratoma, and Rathke cleft cysts may exhibit hypointensities on T2-WI, but other imaging characteristics, clinical and hormonal profiles allow them to be differentiated from prolactinomas [11].

Adenomas of low SI on T2-WI are frequently observed in acromegaly and could translate differences in term of granulation pattern but the clinical characteristics and hormonal profile should easily distinguish them from prolactinomas.

Some studies have tended to associate signal intensity on T2-WI and adenoma consistency. Pierrallini et al. found a correlation between tumor consistency and apparent diffusion coefficient, diffusion-weighted image signal intensity ratio, T2-WI signal intensity ratios, and percentage of collagen content, as soft tumors displayed a lower signal intensity than did intermediate and hard tumors [12]. However Luchi et al. described an inverse correlation between signal intensity on T2-WI and the percentage of collagen content in macroadenomas [13]. More recently, Mahmoud et al. found a strong association between tumor consistency and the percentage of collagen content but no correlation between neither one nor the other and MRI SI [14]. These discrepancies revealed the need of further studies.

In contrast with stellate perivascular deposits, spherical amyloid bodies in adenoma, reported as hypointense areas on T2-WI are rare [15–24]. All cases reported were prolactinomas, except one case of GH-producing adenoma [24] and were predominantly present in men (7 men, 2 women). Among the nine cases of prolactinomas described in literature, CT scan findings were reported in four cases, showing mass containing multiple spheroid-calcified elements [15, 16, 21, 22].

These results are in correlation with our findings. We report CT characteristics in four out of six hypointense T2-WI prolactinomas, all of them showing high-density spots in the pituitary mass. In agreement with the literature on amyloid spheroid deposits, we found a preponderance of hyposignal intensity in pituitary adenoma in men (6 of 39) compared with women (1 of 35). Our hypothesis is that the hypointensities on

T2-WI founded in men prolactinoma in our series and corresponding to high density spots on CT translate a different pattern of prolactinoma almost exclusively encountered in men and correspond most probably to amyloid spheroid deposits. Ultra structurally, the amyloid spherules consist of masses of concentric extracellular amyloid filament bundles that stain positive with congo red. The source of these amyloid deposits in prolactinomas has not been clearly defined, but it may be produced in response to prolactin and composed of fragment of the prolactin molecule [15, 25].

Nevertheless, as we analyze data at the time of diagnosis, we could not exclude that these pattern of hypointensities on T2-WI and corresponding high density spots on CT translate presence of calcification in histological examination. Morphologically, calcifications in pituitary adenomas are generally classified into two groups. In the first type, capsular calcifications outlining the limits of the adenoma are found. These represent a nonspecific deposit within the meningeal investment. The second type is characterized by calcareous concretions within the adenomatous tissue, most frequently in the form of psammoma bodies or calcospherites [26], as encountered in our series. Nevertheless, correspondence between radiological and histological calcifications in pituitary adenomas is quite variable. According to radiological series, incidence of calcifications in pituitary adenomas ranges from 1.2 to 9.4 % and is higher and more variable in histological studies. Moreover, Deery observed no microscopic calcification in 19 adenomas that demonstrated radiological calcifications [27]. Only 18 cases of pituitary stones, characterized by large calcified intrasellar mass and prominent calcification on histological examination are described in the literature [28]. Moreover, formalin fixation is the usual histological method approved in Highman's Congo red technique used for the highlighting of amyloid deposit. However, formalin mixture simultaneously fixes and decalcifies [29]. To confirm this hypothesis in our series, histological results should be provided. However, as medical treatment is the first line therapy and allow PRL normalization and tumor size reduction in most cases, none of our patient underwent surgery.

In any event, we described difference between men and women prolactinomas in signal intensities on T2-WI at the

time of diagnosis and a particular pattern of prolactinoma described as lesions with hypointensities on T2-WI and corresponding high density spots on CT almost exclusively encountered in men. These patterns, in agreement with literature, could translate amyloid spheroid deposit. Distinction of these particular prolactinomas could lead to more accurate diagnosis and better management. Besides, some cases of adenomas with spherical amyloid deposits report lack of decrease in the size of the tumor in case of medical therapy [17, 23] and others reported unusual firm, fibrous consistent in case of transsphenoidal resection [15, 16, 20, 23].

One limitation of our study is the low proportion of macroadenomas in our women subgroup. In consequence, heterogenicity in the men subgroup could be the consequence of the tumoral size at diagnosis.

Further studies are needed to confirm, in larger series, that this characteristic hyposignal on T2-WI translate amyloid spherical deposit and to determine if these prolactinomas present difference in term of aggressiveness or response to dopamine agonist.

Conclusion

Prolactinoma represent the most frequent subtype of pituitary adenomas. Their clinical characteristics and differences at diagnosis between both sexes are already well described.

Our study reports, for the first time, another gender difference at time of presentation. Most prolactinomas in women present with T2 hyperintensity while presentation in men is more heterogeneous. In the latter, presence of T2 hypointensities can be predictive of a different subtype of prolactinoma and of the presence of spherical amyloid deposits.

Ethical standards and patient consent We declare that all human studies have been approved by the comité d’Ethique hospitalo-facultaire du CHU de Liège, Belgique and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patient consent was waived due to the retrospective nature of this study.

Conflict of interest We declare that we have no conflict of interest.

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