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Prolactin levels and gender are associated with tumour behaviour in prolactinomas but Ki-67 index is not

Charakter wzrostu gruczolaków przysadki typu prolactinoma zależy od stężenia prolaktyny i płci pacjentów, ale nie od wartości wskaźnika Ki-67

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Abstract

Introduction: The objective of this study was to investigate the effects of some clinical and pathological features of prolactinomas on tumour behaviour.

Material and methods: The study included 113 patients with prolactinoma (27 male, 86 female), with a mean age at diagnosis of 34.4 ± ± 10.0 years (40.3 ± 12.6 in males, 32.6 ± 8.3 in females). Patients were grouped as invasive or non-invasive according to radiological imaging findings. Ki-67 levels were evaluated if possible.

Results: The mean adenoma size (longest dimension) was 38.6 ± 21.6 mm and 10.8 ± 9.4 mm in male and female patients. Pre-treatment serum levels of prolactin were defined as mean 1,926 ± 6,662ng/mL in all, 124.8 ± 63.4 and 4,675 ± 10,049ng/mL in the noninvasive and invasive groups ($p < 0.05$). A positive correlation was found between the serum levels of prolactin and tumour size. The rate of patients with Ki-67 ≥ 0.03 was 37.5% and 47.8% in the noninvasive and invasive groups. The reduction rates were 60.8% and 80.4% in tumour sizes and 81.1% and 93.8% in prolactin level in the noninvasive and invasive groups, respectively, ($p < 0.05$).

Conclusions: We found a strong correlation between prolactin levels and invasiveness in male patients compared to females. Ki-67 index was not found to have a place in defining the prognosis. **(Endokrynol Pol 2014; 65 (3): 210–216)**

Key words: *prolactinoma; tumour behavior; invasiveness;adenoma size; gender*

Streszczenie

Wstęp: Celem badania była analiza zależności pomiędzy wybranymi danymi klinicznymi i cechami patomorfologicznymi a przebiegiem klinicznym u pacjentów z gruczolakiem przysadki wydzielającym prolaktynę (*prolactinoma*)/lub z gruczolakiem prolaktynowym przysadki

Materiał i metody: Do badania włączono 113 pacjentów, u których rozpoznano guzy typu *prolactinoma* (27 mężczyzn, 86 kobiet). Średni wiek pacjentów w momencie rozpoznania wynosił 34,4 ± 10,0 lat (40,3 ± 12,6 u mężczyzn, 32,6 ± 8,3 u kobiet). Na podstawie badań obrazowych/badań radiologicznych guzów pacjentów podzielono na dwie grupy — z gruczolakami inwazyjnymi i gruczolakami nieinwazyjnymi. Wskaźnik Ki-67 oceniono w tych preparatch, gdzie było to możliwe.

Wyniki: Średni wymiar gruczolaka (mierzony według najdłuższej osi) wyniósł 38,6 ± 21,6 mm u mężczyzn i 10,8 ± 9,4 mm u kobiet. Średnie stężenie prolaktyny w surowicy przed leczeniem wynosiło 1926 ± 6662 ng/ml w całej grupie badanej, 124,8 ± 63,4 w grupie guzów nienaciekających i 4675 ± 10049 ng/ml w przypadku guzów naciekających ($p < 0,05$). Stwierdzono istnienie dodatniej zależności pomiędzy stężeniem prolaktyny w surowicy i wymiarem guza. Odsetki pacjentów, u których wartość wskaźnika Ki-67 była duża (≥ 0,03) wyniosły odpowiednio 37,5% w grupie guzów nienaciekających i 47,8% w grupie guzów naciekających. W grupie nowotworów nienaciekających zmniejszenie wymiarów gruczolaka nastąpiło u 60,8% a zmniejszenie stężenia prolaktyny u 81,1% pacjentów, natomiast w grupie guzów naciekających odpowiednie wartości wyniosły 80,4% i 93,8% ($p < 0,05$).

Wnioski: U mężczyzn stwierdzono istnienie wyraźnej zależności pomiędzy stężeniem prolaktyny w surowicy a charakterem naciekającym guza, czego nie wykazano u kobiet. Wskaźnik Ki-67 nie miał związku z charakterem wzrostu guza. **(Endokrynol Pol 2014; 65 (3): 210–216)**

Słowa kluczowe: *prolactinoma; wzrost nowotworu; naciekanie; wymiary gruczolaka; płeć*

Introduction

Pituitary adenomas are the most common form of intracranial lesions. The prevalence of pituitary adenomas varies between 5 and 20% in all intracranial tumours [1–3]. Prolactinomas are the most common cause of pituitary adenomas, accounting for 60% of the pituitary adenomas causing clinical manifestations. Non-functioning adenomas represent 15%, somatotropinomas 13%, and ACTH-secreting adenomas 6%. The majority of prolactinomas are small microadenomas that can be treated with dopamine agonists; however, they can present different features of biological behaviour and are sometimes seen as macroadenomas or giant adenoma size. Macroadenomas are identified later, with symptoms of visual impairment, headache

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and hypopituitarism more often seen because of extracellular diffusion [4, 5].

The mechanism and definition of aggressive biological behaviour in prolactinomas has not been fully defined. Usually, because of its great size and spread into surrounding tissues, an adenoma is defined as invasive in imaging modalities. Not all aggressive adenomas continue to follow an aggressive course. Although some adenomas are quite invasive during diagnosis, they may be quickly controlled with therapy, being reduced in size and with serum prolactin reduced to normal levels. On the other hand, some prolactinomas are unresponsive to treatment, with uncontrolled serum prolactin levels and may quickly involve the surrounding tissues, despite treatment. Adenomas that are unresponsive to surgical or medical therapies are clinically referred to as aggressive adenomas [6].

Several histopathological evaluations (cell proliferation markers or angiogenesis) have been conducted on the early diagnosis of biologically aggressive adenomas. The results of these studies based on the determinants of cell proliferation are inconsistent with the criteria on clinical aggression [6].

Many studies have reported that serum prolactin level was correlated with the tumour size and invasiveness of the adenoma. Levels of serum prolactin higher than 3,300 ng/mL have been reported to be definitive, with a specificity of 91% (sensitivity was not mentioned) [7]. In another study, the levels of serum prolactin were significantly higher in tumours causing cavernous sinus invasion [8].

In our study, the aim was to investigate the effects of some clinical and pathological features on tumour behaviour in prolactinomas and the effects of differences in tumour behaviour on responses to treatment.

Material and methods

This study included prolactinoma patients, 61 with macroadenomas and 52 with microadenomas, followed up at Uludağ University Department of Endocrinology and Metabolism. Patients' demographic characteristics, pretreatment plasma prolactin levels at the time of diagnosis and sella MR imaging findings, the therapies received and plasma levels of prolactin and sella MR imaging findings until the final polyclinic control were recorded from the archive files. Similar numbers of patients with macroadenomas and microadenomas were included for a reliable comparison. According to the sella MR imaging findings during the diagnosis, the tumours were defined as microadenoma (the longest dimension < 1 cm), macroadenoma (the longest dimension between 1 and 4 cm) or giant adenoma (the longest dimension > 4 cm). The patients were divided into two groups as having non-invasive or invasive tumour. This grouping considered their stage according to Hardy classification and invasion status to the cavernous sinuses. [9]. The invasive properties of the adenomas were graded using Hardy classification. For this purpose, sella base was graded as 1–4 according to the degree of destruction; and between A and E, according to the degree of suprasellar extension, based on the sella MR images [9]. According to the radiological findings, tumours of grades 1–2 and stages A–C stages were included in the non-invasive group, while those of grades 3–4 and stages D–E were classified as invasive. The coronal sections on sella MR images were examined in detail and persistence or absence of cavernous sinus invasion was defined. The adenomas involving 67% (two-thirds) of the segment in the cavernous sinus of internal carotid artery were defined as cavernous sinus invasion and these patients also included in the invasive group [6, 10]. In addition, Ki-67 indices were recorded in line with the histopathological reports of the operated patients in order to evaluate the association of Ki-67 index with the tumour behaviour (in patients for whom Ki-67 levels were measured during histopathological evaluation). The patients with a Ki-67 index ≥ 3/100 were considered as having highly proliferative properties [7].

This study was approved by the Uludağ University, Medical Faculty, Bursa Clinical Research Ethics Committee. All the cases were informed of the aims of the study and provided signed written consent.

SPSS (version 17) was used for statistical analysis. Demographic and clinical data was analysed using descriptive statistics (arithmetic mean, standard deviation) and percentage. The independent t-test, Kruskal-Wallis and Mann-Whitney U analysis of variance were used to evaluate means between groups. The chi-square test was used for comparison of categorical data between groups. Pearson and Spearman correlation analyses were used to examine correlation, where appropriate. P values < 0.05 were considered statistically significant.

Results

The mean age at the time of diagnosis was 34.4 ± 10.0 (16–70) years in 113 patients (27 males, 86 females). The mean age at diagnosis was 40.3 ± 12.6 (19–70) among male and 32.6 ± 8.3 (16–60) among female patients. The mean of adenoma sizes (longest dimension) was 17.9 ± 18.1 (2–80) mm overall, 38.6 ± 21.6 (3–80) mm in male and 10.8 ± 9.4 (2–45) mm in female patients. The rate of operated patients was 44.3% overall and 85.2% among male patients. Male and female patients showed significant differences in terms of age at diagnosis, mean adenoma sizes and rate of operated patients (Table I).

Table I. *General characteristics of the patients according to gender*

Tabela I. *Charakterystyka grupy badanej w zależności od płci*

	Total	Male	Female	p
Number of patients (n)	113	27	86	
Age (years)	40.8 ± 10.1	45.1 ± 12.1	39.5 ± 9.0	0.011
Age at diagnosis (years)	34.4 ± 10.0	40.3 ± 12.6	32.6 ± 8.3	< 0.01
Adenoma size [mm]	17.9 ± 18.1	38.6 ± 21.6	10.8 ± 9.4	< 0.01
Macroadenoma (%)	54.0	85.2	44.2	< 0.01
Giant adenoma (%)	14.2	48.1	3.5	< 0.01
Invasive (%)	39.8	81.5	26.7	< 0.01
Operated rate (%)	44.3	74.1	34.9	< 0.01

The rates of macroadenomas contain the giant adenomas. p values associated with the male and female groups

Table II. *Ages at diagnosis, adenoma size, prolactin levels, Ki-67, high Ki-67 and operated patient rates in noninvasive and invasive groups with gender*

Tabela II. *Wiek pacjentów w momencie rozpoznania, wymiar guza, stężenie prolaktyny, wskaźnik Ki-67, odsetek przypadków ze zwiększonym wskaźnikiem Ki-67 oraz odsetek pacjentów operowanych w grupie guzów naciekających i w grupie bez cech naciekania w zależności od płci*

	Total	Noninvasive	Invasive	p
Number of patients (n)	**113**	**68**	**45**	
Age at diagnosis (years)	34.4 ± 10.0	32.3 ± 7.9	37.6 ± 12.0	0.011
Male	40.3 ± 12.6	40.4 ± 9.5	40.3 ± 13.4	NS
Female	32,6 ± 8,3	31.6 ± 7.5	35.1 ± 10.1	NS
Adenoma size [mm]	17.9 ± 18.1	6.8 ± 3.8	34.7 ± 18.4	< 0.01
Male	38.6 ± 21.6	9.2 ± 9.1	45.3 ± 17.5	< 0.01
Female	10.8 ± 9.4	6.6 ± 3.1	23.1 ± 11.1	< 0.01
Prolactin level [ng/mL]	1,927 ± 6,662	124 ± 63	4,675 ± 10,049	< 0.01
Male	6,818 ± 12,399	138 ± 68	8,576 ± 13,446	< 0.01
Female	402 ± 1,403	123 ± 63	1,147 ± 2,584	< 0.01
Ki-67 index means	0.03 ± 0.02	0.03 ± 0.02	0.03 ± 0.03	NS
Male	0.03 ± 0.02	0.09*	0.02 ± 0.02	NS
Female	0.03 ± 0.02	0.02 ± 0.02	0.03 ± 0.02	NS
High Ki-67 rates (%)	45.1	37.5	47.8	NS
Male	53.8	100.0*	50.0	NS
Female	38.9	28.6	45.5	NS
Operated rates (%)	44.3	17.6	84.4	< 0.01
Male	74.1	20.0	86.4	0.013
Female	34.9	17.5	82.6	< 0.01

*Only one patient; p values associated with the noninvasive and invasive groups

There were 68 patients (60.2%) in the non-invasive and 45 patients (39.8%) in the invasive group. The rate of invasive pituitary adenoma was significantly higher in male than female patients (81.5% *vs.* 26.7%) (Table I). The mean age at diagnosis was 32.3 ± 7.9 (16–54) years, and male to female ratio was 5/63 in the non-invasive group, compared to 37.6 ± 12.0 (18–70) years and 22/23 in the invasive group. When the mean ages and gender ratios were compared, a statistically significant difference was found between the invasive and non-invasive groups. However, the subgroups showed no statistically significant difference in gender ratios between the invasive and non-invasive groups (Table II).

The mean pre-treatment longest diameter of adenomas was 27.8 ± 53.4 mm (2–80 mm) overall; 20.7 ± 22.9 mm (2–25 mm) in the non-invasive group; and 38.4 ± 79.0 mm (10–80 mm) in the invasive group. The mean pre-treatment levels of serum prolactin were 1,926 ± 6,662 ng/mL (650.8 ng/mL after the 5th percentiles were excluded) overall, compared to 124.8 ± 63.4 ng/mL in the non-invasive group and 4.6 ± 10.0 ng/mL (2.9 ng/mL after the 5th percentiles were excluded) in the invasive group.

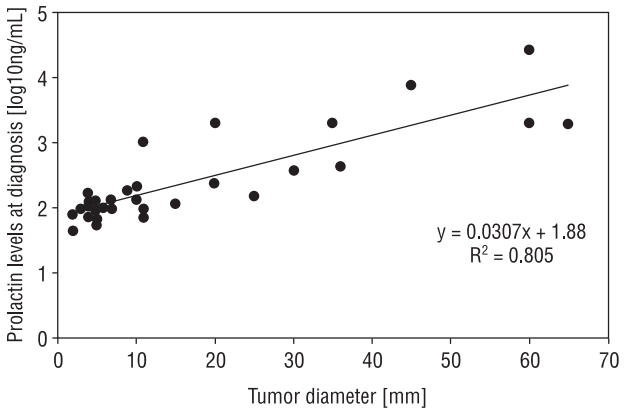

Figure 1. *Correlation between pretreatment prolactin level and longest tumour diameter*

Rycina 1. *Zależność pomiędzy stężeniem prolaktyny i największym wymiarem guza przed leczeniem*

Table III. *Response to treatment in noninvasive and invasive groups*

Tabela III. *Odpowiedź na leczenie w zależności od charakteru guza (nieinwazyjny/inwazyjny)*

	Noninvasive (n = 68)	Invasive (n = 45)	p
Tumour Size			
Before Treatment [mm]	20.7 ± 22.9	38.4 ± 79.0	
After Treatment [mm]	2.33 ± 2.3	7.49 ± 13.5	
Change rate (%)	60.8	80.4	0.02
Prolactin Level			
Before Treatment [ng/mL]	124 ± 63	4,675 ± 10,049	
After Treatment [ng/mL]	6.8 ± 3.8	34 ± 18	
Change rate (%)	81.1	93.8	< 0.01

The longest tumour diameter values and serum prolactin levels were significantly different between the non-invasive and invasive groups (Table II). On the sella MRI imaging taken at diagnosis, microadenoma was identified in 46%, macroadenoma (including giant adenomas) in 54%, and giant adenoma in 14.2% of the patients. Of the macroadenomas, 37.2% were in the non-invasive and 62.8% in the invasive group. The incidence of cavernous sinus invasion was 65.1% among the invasive group. Furthermore, a positive correlation was found between the pre-treatment levels of serum prolactin and tumour size. The correlation coefficient was 0.805 between log10 values of the prolactin levels (ng/mL) and tumour size (mm) (Fig. 1).

Of the 113 patients, 50 were operated upon. There was a secondary operation in three patients following recurrence. Of the 50 operated patients, 12 (24%) were in the non-invasive and 38 (76%) were in the invasive group. The difference between two groups in terms of the rates of operated and non-operated patients was statistically significant, although the patients operated upon were not associated with tumour behaviour, due to lack of sufficient information in the archival files (Tables I, II).

When the 31 patients studied with Ki-67 indices were examined histopathologically, high proliferation values (Ki-67 ≥ 0.03) were found in 14 (45.2%) patients, while Ki-67 indices < 0.03 were defined in 17 (54.8%) patients. Mean age at diagnosis was 38.14 ± 10.0 (n = 14) in the high-Ki-67 group and 32.76 ± 7.5 (n = 17) in the low-Ki-67 group. The proportion of patients with Ki-67 ≥ 0.03 was 37.5% in the non-invasive group and 47.8% in the invasive group. The invasive group had an average Ki-67 value of 0.031 (0.001–0.085), whereas the non-invasive group had 0.033 (0.007–0.097) (p: 0.718). The difference between two groups was not found to be statistically significant (Table II). Three patients (37.5%) in the invasive group and 11 patients (47.8%) in the non-invasive group were categorised as having high Ki-67 index. The incidence of cavernous sinus invasion was 52.9% in the low-Ki-67 group, compared to 50.0% in the high-Ki-67 group.

When the responses to surgical and dopamine agonist therapy were evaluated, rates of tumour reduction were 60.8% and 80.4%, and 81.1% and 93.8% in prolactin level within the non-invasive and invasive groups, respectively. The percentage reduction in prolactin levels and adenoma size were significantly higher in the invasive adenomas compared to non-invasive (Table III). Reduction in tumour size and prolactin level were 75.19% and 90.96%, respectively, in the low Ki-67 group, compared to 86.36% and 88.16% in the high Ki-67 group (p = 0.561, p: 0.922). When the responses to the treatment were evaluated in terms of the Ki-67 cell proliferation indices, no statistically significant difference was found between the groups with high and low indices in terms of the change in tumour size or prolactin level (Table IV).

Discussion

Prolactinomas are by far the most common type of tumours, representing 60% of pituitary adenomas [3]. These are often benign, but may present differences in terms of tumour size and treatment responses at the time of diagnosis due to their different biological behavioural characteristics. In general, prolactin-secreting pituitary adenomas give a very good response to dopamine agonists and both provide improvement of hypogonadism symptoms by enabling serum prolactin to return to normal levels and eliminate compression symptoms by reduction of the adenoma size. In rare cases, pro-

Table IV. *Response to treatment in low and high Ki-67 ratio groups*

Tabela IV. *Odpowiedź na leczenie w zależności od wartości wskaźnika Ki-67 (mały/duży)*

	Ki-67 < % 3 (n = 17)	Ki-67 ≥ % 3 (n = 14)	p
Tumour Size			
Before Treatment [mm]	26.0 ± 16.5	27.9 ± 18.2	
After Treatment [mm]	8.3 ± 15.1	6.2 ± 15.6	
Change rate (%)	75.1	86.3	NS
Prolactin Level			
Before Treatment [ng/mL]	3,465 ± 7,075	4,744 ± 14,269	
After Treatment [ng/mL]	29 ± 38	49 ± 107	
Change rate (%)	88.9	83.8	NS

lactinomas are resistant to treatment with dopamine agonist and these desired outcomes are not achieved.

In this study, mean serum prolactin levels were 38.4 ± 79.0 and 4,675.8 ± 10,049.2 ng/mL in the non-invasive and invasive groups, respectively. There was a statistically significant positive correlation between the pre-diagnosis prolactin levels and tumour size (R: 0.805, $p < 0.01$). As expected, these findings show serum prolactin level to be an important factor in the definition of tumour behaviour. In a study by Lundin et al. [11] with 115 hypophysis macroadenoma cases, the size and invasiveness of the tumours were evaluated from MR imaging with hormonal activity, and the strongest correlation was found between the tumour size and prolactin level in the patients with prolactinoma. In a study by Raverto et al. [12], 91 operated prolactinoma patients were evaluated and the mean preoperative prolactin levels were found to be 262 ± 532 and 1,633 ± 1,890 μg/L in the non-invasive and invasive adenomas, respectively. In a study by Calle-Rodrigue et al. [7], the mean preoperative prolactin levels were 705 ng/mL in the invasive and 141 ng/mL in the non-invasive prolactinomas. In that study, the cut-off value of 3,300 ng/mL for the serum prolactin level was reported to have a sensitivity of 91% in the definition of the invasive prolactinomas. In our study, when cases with a serum prolactin level higher than 3,300 ng/mL were examined (n:8), all were in the invasive adenoma group. Of patients with a lower serum level of prolactin, 61 were in the non-invasive and 32 in the invasive group. When the cut-off value was taken as 400 ng/mL, sensitivity was calculated as 70% and specificity as 100%.

In our study, the mean tumour size was 38.6 ± 21.6 (3–80) mm in the male patients and 10.8 ± 9.4 (2–45) mm in the female patients. The rates of invasive pituitary adenomas, macroadenomas and giant adenomas were significantly higher in the male than in the female patients. The age of diagnosis was significantly higher in the male compared to the female patients. In this study, 81% (13/16) of the giant adenomas were in the male patients. Delgrange et al. [13] examined the association between tumour size and proliferative properties according to gender (96 prolactinoma cases; 45 males and 51 females). Basal prolactin levels and tumour diameters were higher in the males than females ($p < 0.001$). In a retrospective study by Nishioka et al. [14] with 51 prolactinoma patients (16 males, 35 females), large tumours were predominant in the male patients, and these patients were more likely to develop cysts and haemorrhaging. Furthermore, the correlation between prolactin level and tumour size was less significant among male than female patients, but the difference was eliminated after patients with cystic and haemorrhagic masses were excluded. The results from our study indicate, as expected, that male gender is a determinant factor in tumour properties. However, it is unclear whether the difference seen in male patients regarding the diameter and invasiveness of the tumour is caused by a difference in the tumour formation or by a later diagnosis in male patients.

The age of diagnosis in our patients was significantly higher for invasive than non-invasive adenomas. However, the rates of male patients were also higher in the invasive group and, as mentioned previously, the association of male gender with invasiveness and size of tumour is widely accepted. It was reported by Delgrange et al. [13] that age at diagnosis and symptom duration was not associated with prolactin level and tumour size. Another study by the same author investigated the effect of age on male prolactinoma patients; basal prolactin levels (3.051 ± 4.151 *vs.* 3.365 ± 4.949 μ/L) and the mean tumour diameter (30 ± 16 *vs.* 25 ± 13 mm) were found to be similar in nine elderly and ten young patients [15]. In a study by Raverot et al. [12], the mean preoperative age was 33.4 ± 10.9 in the non-invasive group (n: 61; 64.9%), 43.3 ± 11.5 in the invasive group (n: 22, 23.4%) and 51.5 ± 10.4 in the invasive-aggressive group (n: 11; 11.7%). However, the mean ages of the subgroups according to gender were not given in that study, and there were more male patients with invasive adenomas compared to the non-invasive group. Accordingly, age is not an independent factor in the invasiveness or size of tumours and age-related differences are associated with older age at diagnosis in the male patients.

In the WHO classification of endocrine tumours, pituitary adenomas with Ki-67 index and p53 immune reactivity > 3% are classified as atypical adenomas. In a study by Thapar et al. [16], Ki-67 values were evaluated in 37 non-invasive adenomas, 33 invasive adenomas and seven primary hypophysis carcinomas, and the mean values were 1.3%, 4.6% and 11.9%; respectively ($p < 0.01$). In that study, Ki-67 index with a cut-off value > 3% was reported to have a sensitivity of 97% and specificity of 73% in differentiation between invasive and non-invasive tumours. On the other hand, in the study by Delgrange et al. [13], no significant difference was identified between invasive and non-invasive groups in terms of Ki-67 index values in 45 male and 51 female patients with prolactinomas. In a study by Scheithauer et al. [17] with 153 hypophysis tumour cases, Ki-67, PCNA indices and p63 expressions of tumour tissue were evaluated; no significant difference was found between the non-invasive and invasive tumours. In a study by Paek et al. [18] with 44 hypophysis macroadenoma cases, a high Ki-67 index was correlated with visual field defect and rates of tumour recurrence, while there no statistical difference regarding tumour diameter, tumour degree, Hardy classification and cavernous or sphenoid sinus invasion.

In our study, evaluation of Ki-67 index values could be carried out in pathological materials of 31 patients. In the evaluation, the mean Ki-67 indices in the non-invasive and invasive prolactinomas were very similar, at 0.033 ± 0.03 and 0.031 ± 0.02, respectively. Ki-67 index was higher than 3% in three patients (37.5%) in the invasive group and 11 patients (47.8%) in the non-invasive group. According to these results, Ki-67 index was not a prognostic determinant in the prolactinoma patients.

The objective of defining the properties of tumour behaviour is to identify treatment unresponsiveness and the risk of recurrence. A decrease of less than 50% in prolactin level or tumour size compared to the baseline values is considered as unresponsive [19]. In our study, treatment responses were evaluated by examination of the changes in the basal and final prolactin levels and the percentage change in the adenoma size. Accordingly, no significant difference was found between patients with a Ki-67 index ≥ 3% and those with a low Ki-67 index, in terms of changes in the prolactin levels and adenoma sizes. In a study by Wu et al. [20], a mean decrease of 93% in the tumour diameter was reported at 37 months follow-up of bromocriptine therapy in giant prolactinomas. In a study by Delgrange et al. [21] with 122 macroprolactinoma cases, the need for higher doses of cabergoline was reported in male patients and/or invasive tumours, but normalisation in the prolactin level was reported in 94% of patients.

The results from our study also indicate that the type of invasive tumour or high cellular proliferation does not negatively affect treatment outcomes; even the decrease in prolactin levels and adenoma sizes was found to be higher in the invasive tumours.

These findings show that treatment response is not poorer in the presence of invasion in prolactinomas, and that proportionally better outcomes may even be obtained. These rates do not suggest curative outcomes in the long term, but indicate that the treatment approach is not necessarily different in invasive tumours. The treatment response in prolactinomas is thought to be more closely related to changes in cellular D2 receptors [22].

Conclusions

In this study, as indicated by previous studies, a strong correlation was found between prolactin levels and the size and invasiveness of tumours. The size and invasiveness of the tumours were significantly higher in male compared to female patients. However, no definitive role was identified for prolactin levels, tumour sizes, invasiveness or gender in terms of treatment response.

In our study, the mean of Ki-67 indices were found to be similar in invasive and noninvasive groups. Furthermore, Ki-67 indices were not found to be related to treatment response. Accordingly, in determining the behaviour of the tumour in prolactinomas, Ki-67 index cannot play a decisive role.

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