Evaluation of atherosclerosis after cessation of cabergoline therapy in patients with prolactinoma

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ABSTRACT

Objective: The aim of the study was to determine whether atherosclerotic risk markers exist at the moment and after withdrawal of cabergoline (CAB) therapy in patients who had taken a suitable dose of CAB therapy for a suitable period of time before cessation of CAB.

Methods: This study was designed as prospective cross-sectional. Out of a total of 115 patients with prolactinoma, 42 non-obese women with microprolactinoma, who met the Pituitary Society criteria (2006) for the withdrawal of long-term CAB therapy, and 30 healthy patients participated in our study. The number of patients excluded from the study were as follows: 34 patients with tumor shrinkage of less than 50%; 10 who received DA treatments for less than 2 years; 9 who were treated with bromocriptine; and 20 who had diabetes mellitus, hypertension, hyperlipidemia, obesity, renal disease, coronary arterial disease, or were tobacco smokers. The patients were evaluated for anthropometric, metabolic, and inflammatory parameters at the time of cessation of CAB therapy and at the 3rd and 12th months after the withdrawal of CAB therapy. Endothelial dysfunction was determined by flow-mediated dilation (FMD) of the brachial artery and carotid intima media thickness (IMT), which were assessed by high resolution ultrasonography (USG) by the same practitioner.

Results: At the moment of cessation of CAB therapy, the FMD percentage in patients with prolactinoma was worse than that in healthy controls (p=0.0029). After the withdrawal of CAB treatment, fibrinogen (p=0.036), mean platelet volume (MPV) (p<0.001), carotid IMT (p=0.041), and high-density lipoprotein cholesterol (HDL C) (p=0.048) were worse in the relapse patients than those in the remission patients. Furthermore, only MPV values were found to be significantly related to a relapse of hyperprolactinemia among all atherosclerotic risk markers [area under the curve: 0.830 (95% CI 0.685–0.974) (p<0.001)].

Conclusion: Unfavorable cardiovascular risk profiles are a problem for patients with prolactinoma during cessation and after CAB withdrawal. *(Anatol J Cardiol 2016; 16: 440-7)*

Keywords: atherosclerotic risk markers, prolactinoma, relapse of hyperprolactinemia

Introduction

Prolactinomas are common pituitary tumors, 90% of which are microprolactinomas (1). Most prolactinomas can be successfully treated medically. The aims of medical therapy are to improve gonadal function and control symptoms such as oligomenorrhea, amenorrhea, infertility, and galactorrhea (2). Dopamine agonists (DA) suppress prolactin (PRL) secretion and decrease adenoma size in patients with prolactinomas (2-4). The effects of DA therapy cessation on the relapse of hyperprolactinemia have been assessed in several studies (5-8). Recently, some studies were performed to determine the optimal timing for cabergoline (CAB) withdrawal (5, 6). The 2006 Endocrine Society Clinical Practice Guideline concerning the diagnosis and treatment of hyperprolactinemia recommends DA withdrawal in patients with normal serum PRL who have been treated for at least 2 years and who have either no visible tumor remnant on magnetic resonance imaging (MRI) or at least a 50% reduction in adenoma size (9).

Hyperprolactinemia has been related to impaired metabolism, atherosclerosis, dyslipidemia, hypercoagulability, and impaired endothelial function (10-12). Some studies have indicated an association between atherosclerotic risk markers and hyperprolactinemia in subjects with untreated prolactinomas (13, 14). In these studies, direct carotid intima media thickness (IMT) or other factors that promote atherogenesis, including insulin resistance, low-grade inflammation, and endothelial dysfunction, were evaluated (13, 14). Similarly, some studies have demonstrated an increase in thrombosis frequency in patients with untreated prolactinoma (14, 15). On the other hand, it is not known whether endothelial dysfunction exists in prolactinoma patients undergoing remission or relapse. Recently, the impact

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of atherosclerotic risk markers for endothelial dysfunction was demonstrated in the AACE 2012 Lipid and Atherosclerosis guidelines (16). These markers include new markers such as the ratio of total cholesterol to high-density lipoprotein cholesterol (TCol/HDL-C) as well as old markers, including high sensitivity C-reactive protein, homocysteine, uric acid, lipid parameters, carotid IMT, and flow-mediated dilation (FMD) of a brachial artery. In addition to these markers, several reports over the last decade have indicated that there is a close relationship between high mean platelet volume (MPV) and cardiovascular risk factors (17) such as obesity (18), diabetes mellitus (19), hypertension (20), acute coronary syndrome (21), and stroke (22). Mean platelet volume, the most commonly used measure of platelet size, is a potential marker of platelet reactivity. Larger platelets are metabolically and enzymatically more active and have greater prothrombotic potential (23). A recent study indicated that MPV value in women with prolactinoma was higher than that in healthy controls (24). Moreover, the study found a positive correlation between MPV and PRL levels. Finally, authors of the study acclaimed that elevated MPV may have an impact on atherothrombosis in patients with prolactinoma.

Our study aimed to obtain more insights on the assessment of atherogenic risk factors, including classical markers, endothelial function tests, and new markers (MPV and TCol/HDL) in prolactinoma patients at the time of cessation of CAB therapy and after withdrawal therapy. Another aim was to examine the relapse of hyperprolactinemia and whether it leads to atherosclerosis.

Methods

This prospective study was undertaken at the Endocrinology and Metabolism disease clinic of Ankara Numune Training and Research Hospital between May 2011 and January 2014.

Ethics committee

Institutional Review Board approval for the study was obtained, and patients were asked to sign an informed consent before they enrolled in the study.

Inclusion criteria

From a group of 115 patients with prolactinoma, 42 non-obese women with microprolactinoma who met the Pituitary Society criteria (9) for the withdrawal of long-term CAB therapy participated in our study. Additionally, 30 age-, sex-, and weight-matched healthy volunteer controls participated in our study. Records of 115 consecutive patients with microprolactinoma and were followed for prolactinoma were reviewed. At the time of prolactinoma diagnosis, the patients did not have a hypophysis hormone deficiency, except hypogonadism.

Criteria for cabergoline withdrawal (8)

1) All patients were treated for at least 36 months, and they were in remission for 24 months before the withdrawal of CAB therapy.

a) Improvement of symptoms such as oligomenorrhea, amenorrhea, galactorrhea, and infertility over a period of at least 2 years.

b) PRL levels under the normal range (<20 ng/mL) with the lowest CAB dose over a period of at least 2 years.

2) Normal MRI or ≥50% tumor shrinkage of the baseline diameter (presenting >5 mm from the optic chiasm) and no invasion of the cavernous sinus or sphenoid sinus.

Exclusion criteria's

The number of patients excluded from the study were as follows: 34 patients with tumor shrinkage of less than 50%; 10 who received DA treatments for less than 2 years; 9 who were treated with bromocriptine; and 20 who had diabetes mellitus, hypertension, hyperlipidemia, obesity, renal disease, coronary arterial disease, or were tobacco smokers.

Patients had not received anything apart from CAB, especially oral contraceptives, during the duration of CAB therapy. None of the participants had also taken any drug therapy, including statins, niacins antiplatelets, beta blockers and ACE inhibitors, and systemic anticoagulants.

Study design

This study was designed as prospective cross-sectional.

Main outcomes

1) To determine whether atherosclerotic risk markers exist at the moment of therapy cessation and after withdrawal of CAB therapy.

2) To determine the remission rate of hyperprolactinemia and predictive markers for relapse of hyperprolactinemia.

Patients with prolactinoma were assessed three times on specific visits, including at the moment of CAB therapy cessation and 3 months and 12 months after withdrawal therapy. However, PRL levels were frequently assessed, including at the moment of cessation of CAB therapy and then every month for the first 6 months, quarterly for the next 6 months, and/or when symptoms of hyperprolactinemia relapsed in whom cessation of CAB therapy. If PRL returned above the reference range (>20 ng/mL), another measurement was performed within 1 week and symptoms were assessed. An MRI was performed if the symptoms relapsed and PRL levels were >100 mg/dL (9). A relapse of prolactinoma was diagnosed with high PRL levels that were above the normal range and the presence of hyperprolactinemia symptoms such as oligomenorrhea, amenorrhea, or galactorrhea. However, recurrences of menstrual irregularities were observed only in patients who were restarted on CAB therapy and discharged from the follow-up regime.

Biochemical analyses

Blood samples were taken for FSH, LH, PRL, high sensitive C-reactive protein, homocysteine, fibrinogen, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipopro-

Table 1. Results of the measurements of atherosclerotic risk markers in patients with prolactinoma at the time of cessation of CAB therapy and in the healthy control subjects.

	Patient group (n=42) Mean±SD or median (IQR)	Control group (n=30) Mean±SD or median (IQR)	*P*
Age, years	38 (32–42)	35 (31–41)	0.453
BMI, kg/m^2	27.5 (23–30)	24 (22–27)	0.059
WC, cm	78 (23–130)	69 (68–79)	0.263
FSH, mIU/mL	5.6 (4.2–15.6)	5.4 (4.2–6.3)	0.564
LH, mIU/mL	6.5 (3.3–9.8)	11.8 (6.3–18)	0.067
E2, pg/mL	64 (46–145)	51 (43–102)	0.191
PRL, ng/mL	16 (4.5–18)	12 (9.2–18)	0.214
Hs-CRP, mg/L	0.65 (0.3–3.23)	1.71 (0.74–2.91)	0.155
Fibrinogen, mg/dL	327±78	377±57	0.091
Homocysteine, µmol/L	8.5±3.1	7.4±2.3	0.340
Uric acid, mg/dL	4 (3.5–4.6)	4.6 (3.5–5.6)	0.105
HOMA-IR	1.8±1.08	1.6±1.3	0.339
LDL-C, mg/dL	97±25	97±26	0.76
HDL-C, mg/dL	55 (45–62)	56 (45–66)	0.381
TC/HDL-C	3.3±0.92	3.04±0.95	0.133
MPV, fL	9.8±1.5	11.7±0.78	0.001
Carotid IMT, mm	0.78±0.1	0.7±0.13	0.228

BMI - body mass index; carotid IMT - carotid intima-media thickness; E2 - estradiol; FMD - flow-mediated diameter; FSH - follicule-stimulating hormone; hs-CRP - highly sensitive C-reactive protein; HOMA-IR - homeostasis model assessment of insulin resistance; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; LH - luteinizing hormone; PRL - prolactin; WC - waist circumference

tein (HDL-C) and MPV at the time of cessation of CAB therapy and recurrence of the microprolactinoma. Body mass index (BMI) (kg/m^2) was also calculated at the time of cessation of CAB therapy and recurrence of microprolactinoma.

Assays

FSH (mIU/mL), LH (mIU/mL), estradiol (E2) (pg/mL), and PRL (ng/mL) were studied using the immune chemiluminescent method [Unicel DxI 800 System immune-analyzer (Beckman Coulter Ireland Inc., Ireland]. Lipid parameters were determined by the colorimetric method using a UniCel DxC 800 Systems autoanalyzer (Beckman Coulter, Fullerton, CA) with original reagents. Insulin (mcIU/mL) was analyzed using chemilumunescende paramagnetic particle immunoassays (Unicel DxI 800 System, Beckman coulter, Brea, CA). Total blood count, including MPV (fL), was measured using the Coulter cellular DxH 600 analyzer (Beckman coulter, Brea, CA). High-sensitivity CRP was measured with the Roche Cobas C 501 device by the immunoturbidimetric method. Homocysteine was measured with the HP Agilent device via high-performance liquid chromatography (HPLC).

Magnetic resonance imaging

Pituitary morphological evaluation was performed using 3 Tesla Dynamic MRI (Siemens, Germany) before the cessation of CAB therapy and when PRL levels rose above 100 mg/dL again (9) and/or in the presence of menstrual irregularities.

Measuring insulin resistance

Insulin resistance (IR) was calculated using the homeostasis model assessment of insulin resistance [HOMA-IR: fasting blood glucose (mg/dL)**x**fasting insulin (µIU/mL)/405] method. Values of HOMA-IR >2 were regarded as IR (25).

Non-invasive measurements of arterial structure and function tests

Endothelial function tests, including carotid IMT and brachial artery FMD, were performed in fasting state between 8 A.M. and 12 A.M. in a supine position after 20 min at rest by an experienced endocrinologist via high resolution B-mod ultrasonography (USG) (Hitachi EUB 800, UK) in patients with prolactinoma at baseline (26) and healthy subjects. The same investigator who was blinded to the study protocol repeated the ultrasound examinations in patients with prolactinoma.

Carotid IMT measurements were performed at three sites of the right and left carotid artery and then were averaged for calculation. A standardized FMD methodology was used (27). The brachial artery of the right arm was first visualized longitudinally and then stabilized in this position. The baseline brachial artery diameter was measured from the inter-intima to intima in end-diastole (identified by the R wave on electrocardiography over 10 cardiac cycles) (27). After three baseline measurements were obtained, a cuff was inflated 25–50 mm Hg above systolic arterial pressure for 5 min (27). Then, the cuff was deflated to cause reactive hyperemia and to release nitric oxide from the endothelium. After the deflation of the cuff, peak diameter measurements were performed after 2 min (27). FMD was calculated using the formula: FMD (%) = (peak diameter-baseline brachial diameter)/baseline brachial diameter x 100) (27).

All subjects were advised not to consume caffeine and to avoid smoke exposure and exercise during the prior 12 h.

The Bland–Altman method was used to determine the intra-observer variability for repeated measurements of carotid IMT and FMD%. Intra-observer variability in measurements of the carotid IMT and FMD% were first assessed by the same investigator in a pilot population. The mean biases for the carotid IMT and FMD% were -0.008±0.082 (95% CI: -0.090–0.074) and 0.067±6.590 (95% CI: -6.523–6.657), respectively.

Statistical analyses

The Shapiro–Wilk and Kolmogorov–Smirnov tests were performed to test for the normal distribution of variables. The Student's t-test and one-way repeated measures analysis of variance (ANOVA) were performed to compare independent variables that were normally distributed, and the variables were

Table 2. The effects of cessation of the CAB therapy on atherosclerotic risk markers in patients with prolactinoma. The values of the atherosclerotic risk markers at the time of cessation of CAB therapy were shown as "first measurement," whereas the values in relapse measurements recorded 3 and 12 months after cessation of CAB therapy were shown as "second measurement" and "third measurement."

	First measurement Mean±SD median (IQR) (n=42) (no therapy)	Second Measurement Mean±SD median (IQR) (n=42) (no therapy)	Third Measurement Mean±SD median (IQR) (n=36) (no therapy)	*P*
BMI, kg/m^2	27.2±4.4	27.3±4.4	27.7±4.06	0.290
WC, cm	78 (68–80)	75.5 (67–80)	76 (69–82)	0.192
PRL, ng/mL	16 (4.5–18)	45 (26–69)*	55 (24–69)*	<0.001
Tumour volume, mL	5.3±7.7	5.2±2$^{\#}$(n=6)		
hs-CRP, mg/L	0.65 (0.3–3.23)	0.6 (0.47–6.1)	1.1 (0.57–5.3)	0.069
Fibrinogen, mg/dL	327±78**	339±87	363±80	0.036
Homocysteine, umol/L	8.5±3.1	8.9±2.9	8.08±2.3	0.076
Uric acid, mg/dL	4 (3.5–4.6)	4 (3.3–4.5)	4(3.4–4.2)	0.930
HOMA-IR	1.8±1.08	2.02±1.2	2.09±1.3	0.90
HDL-C, mg/dL	55 (45–62)	53 (43–63)	61 (48–66)	0.417
TC/HDL-C	3.3±0.92	3.2±0.9	3.2±0.8	0.248
MPV, fL	9.8±1.5***	12.7±15.1	11.3±1.0	<0.001
Carotid IMT, mm	0.78±0.1	0.72±0.14	0.71±0.12	0.861
FMD, %	4.09±19	3±19	4±15.8	0.437

*The difference between the first and second/third measurements was statistically significant (p<0.001, p=0.004; correction of Bonferroni, respectively)
**The difference between the first and third measurements was statistically significant (p=0.009, p<0.001 correction of Bonferroni)
***The difference between the first and second/third measurements was statistically significant (p<0.001, p<0.001; correction of Bonferroni, respectively)
#As regard the study protocol in which were described in the main document
BMI - body mass index; Carotid IMT - carotid intima-media thickness; E2 - estradiol; FMD - flow-mediated diameter; FSH - follicule-stimulating hormone; hs-CRP - highly sensitive C-reactive protein; HOMA-IR - homeostasis model assessment of insulin resistance; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; LH - luteinizing hormone; PRL - prolactin; WC - waist circumference

expressed as mean±standard deviation (SD). The independent variables, which were non-normally distributed, were tested using Mann–Whitney's U test for the comparison of two groups and Kruskal–Wallis tests for the comparison between three groups. They were expressed with median and interquartile (IQR) range. The dependent variables were evaluated using Friedman's test for non-normally distributed variables and repeated measures of ANOVA for normal distribution of variables. Receiver operating curve (ROC) analysis was performed to establish the diagnostic value of variables. The Bland–Altman method was used to assess the intra-observer variability in the FMD% and carotid IMT, and mean differences are expressed as mean±2SD. The Statistical Package for the Social Sciences (SPSS) 11.0 (SPSS Chicago, IL, USA) was used for statistical analysis. An alpha value of 0.05 was accepted as statistically significant.

Results

Patient characteristics

The follow-up period and CAB therapy of patients with prolactinoma were prescribed for a period of 5 years (range: 3–12). The mean age of the patients at the time of diagnosis was 30±7.4 years (range: 18–43), and serum PRL levels and tumor volume were 91 ng/mL (range: 71–155) and 18.7 mL, respectively.

Atherosclerotic risk marker comparisons in patients with prolactinoma at the time of cessation of CAB therapy and in controls are shown in Table 1. Among all atherosclerotic risk markers, MPV was lower and FMD% was worse in patients with prolactinoma at the moment of cessation of CAB therapy compared with controls. Serum PRL levels and tumor volumes at the time of CAB withdrawal are shown in Table 2.

Rates of remission

Twelve months following withdrawal of CAB therapy, 19% (8 of 42) of the patients remained normoprolactinemic, whereas 81% (34 of 42) of the patients relapsed with elevated serum PRL levels. Among the relapse group, all 34 patients had already relapsed within 3 months. At 12 months, these patients remained with elevated PRL during the remainder of the 12-month monitoring period. No patients who had relapsed were found to have serum macroprolactinemia. The relapse of oligomenorrhea and hyperprolactinemia occurred in only 14% (6 of 42) of the patients at 3 months. Only these patients were restarted on CAB therapy and were subsequently excluded from the assessment of the atherosclerotic risk markers at 12 months.

An MRI was performed on patients with a relapse of hyperprolactinemia (PRL levels >100 mg/dL) and in those with menstrual irregularities (n=6) after withdrawal of CAB therapy. Mean tumor volume was not different between the time of cessation of

Table 3. Comparison of some characteristics that may be predictive of a relapse of hyperprolactinemia which in the past-time shown, after cessation of CAB therapy in patients with prolactinoma

Characteristic	Remission (n=8) At the time of diagnosis Mean±SD or median (IQR)	Relapse (n=34) At the time of diagnosis Mean±SD or median (IQR)	*P*
Pre-treatment TV, mL	15.3±5.5	22±11	0.264
Pre-treatment	103±63	128±70	0.370
Prolactin, ng/mL	37±5.3	36±7.5	0.732

Median (interquartile range). TV-tumor volume

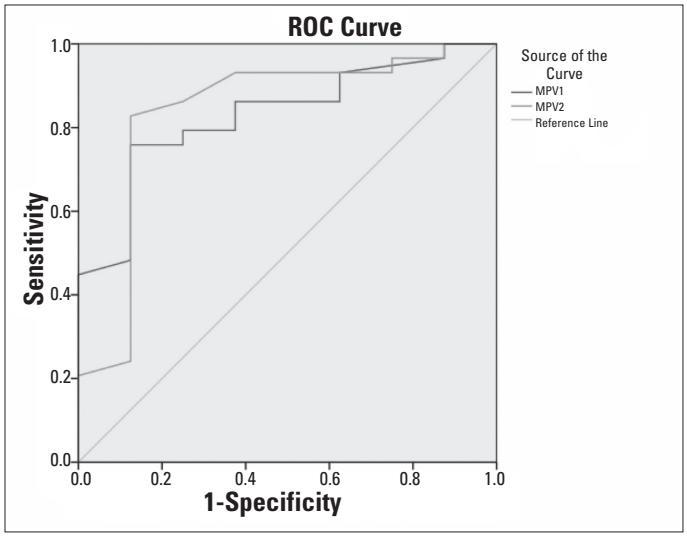

Figure 1. ROC curve analyzes for MPV in patients with a relapse of hyperprolactinemia and oligomenorrhoea

therapy and the recurrence for these patients (5.2±2 mL, 4.8±0.9 mL, p=0.666, respectively).

There were no significant associations between patients with a relapse and remission of hyperprolactinemia after 3 months of withdrawal of CAB therapy with respect to age, serum PRL, or tumor size at the time of diagnosis (Table 3). In addition, there was no difference in the relapse of hyperprolactinemia between the patients whose tumors were still visible or not visible at the time of cessation of CAB therapy (p=0.264).

Correlation analyses

A positive correlation between MPV values and PRL levels was found among atherosclerotic risk markers in patients with a relapse of hyperprolactinemia (p=0.035, r=-0.380).

ROC analysis

Only MPV values were predictive for relapses of hyperprolactinemia among atherosclerotic risk markers. In evaluating patients with prolactinoma with relapses, two ROC curves were constructed to assess the diagnostic value of MPV. The first MPV level was measured at the time of cessation of CAB therapy, and the second MPV level was measured at the time of relapse of hyperprolactinemia. In the first analysis, the area under the curve was 0.830 (95% CI 0.685–0.974, p<0.001), and when the MPV level was taken, the level was 9.75 fL with a sensitivity of 75.9% and a specificity of 87.5% (Fig. 1). According to the second MPV measurement, the area under the curve was 0.841 (95% CI 0.660–1.000, p<0.001), and when the MPV level was taken, it was 9.7 fL with a sensitivity of 82.8% and a specificity of 87.5% (Fig. 1).

Table 4. Comparision of atherosclerotic risk markers between the patients with relapse and remission of hyperprolactinemia in patients with prolactinoma 12 months after withdrawal of CAB therapy

Characteristic	Remission (n=8)	Relapse (n=34)	*P*
BMI, kg/m^2	24.6±3.2	27.1±4.08	0.631
WC, cm	68 (67–73)	78 (67–81)	0.084
PRL, ng/mL	16 (4.5–18)	45 (26–69)	0.043
Hs-CRP, mg/L	0.52 (0.5–0.7)	1.4 (0.44–3.6)	0.953
Fibrinogen, mg/dL	362±85	308±106	0.153
Homocysteine, µmol/L	8.4±1.5	9.09±3.2	0.760
Uric acid, mg/dL	3.8 (3.3–4.15)	4 (3.3–4.9)	0.564
HOMA-IR	1.6±0.9	2.17±1.34	0.717
LDL-C, mg/dL	98±25	108±33	0.786
HDL-C, mg/dL	53 (37–63)	51 (42–64)	0.048
TC/HDL-C	3.5±0.96	3.2±0.92	0.691
MPV, fL	9.15±1.28	13.6±16.9	0.460
Carotid IMT, mm	0.63±0.08	0.75±0.15	0.041
FMD, %	5.2±26.3	7.6±15.7	0.519

BMI - body mass index; Carotid IMT - carotid intima media thickness; E2 - estradiol; FMD - flow-mediated diameter; FSH - follicule-stimulating hormone; hs-CRP - highly sensitive C-reactive protein; HOMA-IR - homeostasis model assessment of insulin resistance; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; LH - luteinizing hormone; PRL - prolactin; WC - waist circumference

Atherosclerotic risk markers in patients with both relapse and remission

Atherosclerotic risk markers of the patients who had a cessation of CAB therapy at 3 months and 12 months after withdrawal of therapy are shown in Table 2. During the follow up, only fibrinogen levels (p=0.036, p<0.001) and MPV values were progressively elevated (p<0.001, p<0.001) at 3 months and 12 months after the withdrawal of therapy, respectively. However, carotid IMT values and FMD percentages were not changed significantly in patients with prolactinoma (Table 2). Similarly, during the follow up, the frequency of high HOMA-IR levels (>2) and hs-CRP levels were elevated, but these were not statistically significant (Table 2).

Comparisons of atherosclerotic risk markers between the relapse and remission of hyperprolactinemia in patients with prolactinoma after 12 months of CAB withdrawal are shown in

Table 4. All atherosclerotic risk markers, except for HDL and carotid IMT, were not different between relapse and remission of patients with hyperprolactinemia. The HDL values were lower in patients with a relapse of the disease (p=0.048), whereas carotid IMT was higher in patients with a relapse of hyperprolactinemia than that in patients with remission (p=0.041). These results are displayed in Table 4.

Discussion

Based on the recent findings, hyperprolactinemia is associated with atherosclerosis and metabolic abnormalities. Our study showed for the first time that endothelial dysfunction, including carotid IMT and FMD percentages, was still worse in patients with prolactinoma than that in healthy subjects at the moment of cessation of CAB therapy. However, to date, the relationship between atherosclerotic risk markers, including carotid IMT, insulin resistance, triglyceride levels, hs-CRP levels, and hyperprolactinemia, have been evaluated only in untreated patients with prolactinoma (13, 14, 27, 28). Our study also revealed that during the follow-up a year after withdrawal of CAB therapy, some atherosclerotic risk markers such as fibrinogen levels and MPV values had progressively increased. For the first time, HDL-C and carotid IMT were found to be worse in patients with relapsed hyperprolactinemia than those in patients in remission 12 months after withdrawal of CAB therapy in our study. Therefore, compared with healthy subjects, our study demonstrated that unfavorable cardiovascular risk profiles are still a problem for patients with prolactinoma at the moment of cessation of CAB therapy, in accordance with the recent guidelines (9).

Hyperprolactinemia is the most common endocrinological disorder responsible for menstrual irregularities. It most commonly affects young women at a fertile age and is treated worldwide with DA and especially with CAB therapy (29). The optimal duration of CAB therapy for microprolactinomas is controversial, and the high recurrence rate of the disease is an important problem after the cessation of the therapy. Thus, several clinicians think that lifetime CAB therapy is necessary. Our study showed that 12 months after CAB withdrawal, 81% (34 of 42) of patients experienced a relapse with elevated serum PRL levels above the normal range, and all of these 34 patients had already relapsed at the 3rd month of withdrawal. Several studies with varying sample sizes and durations of CAB therapy have similarly demonstrated that relapses of hyperprolactinemia occur in 52–90% of microprolactinomas, commonly after 3 months following DA withdrawal (9, 30-35). However, one study revealed lower relapse rates (32%) than the other abovementioned studies; these lower rates may be associated with more rigorous criteria for the withdrawal of CAB therapy, which included no visible tumor (8). There is no consensus on the duration of therapy. However, several criteria, including improvements in PRL levels after CAB withdrawal, and no visible tumor on MRI or at least a 50% reduction in tumor size after at least 2 years of therapy are recommended in the guidelines of the Pituitary Society (9). Very few studies suggest that there are some parameters that can predict the relapse at the time of CAB therapy withdrawal; these parameters can be used to make a decision about discontinuing CAB therapy (36, 37). In contrast to one study (7) and in agreement with several previous reports (30, 31), we did not observe any significant differences in pretreatment PRL levels between patients who achieved remission and those who did not. In addition, there was no elevated risk for a relapse of hyperprolactinemia in our patients whose tumors were still visible, similar to that in one study (8). However, some larger studies have demonstrated that if the tumor was still visible, the risk for a relapse of hyperprolactinemia was higher than that if no tumor was visible (8, 31). Therefore, it can be said that a low-to-normal PRL level before the interruption of therapy and a reduction in tumor size are necessary, but not sufficient, to ensure remission.

Moreover, for the first time, this study has revealed that some atherosclerotic risk markers were higher in patients with a relapse of hyperprolactinemia than those in patients with remission. Considering the past and present results about the relationship between atherosclerosis and prolactinoma, it has been shown that relationships exist in patients with both lacking in treatment and in post-treatment prolactinoma. The importance of atherosclerosis in prolactinoma is a topic which was recently demonstrated by some studies (13, 14, 27, 28). We think that this relationship, which related to atherosclerosis and prolactinoma, should be considered in the follow-up treatment of prolactinoma and in deciding when to withdraw the treatment. The decision is an important entailment for prolactinoma, which is currently investigated by some studies. Furthermore, our study showed that MPV values were found to be predictive for patients with a relapse of hyperprolactinemia among all atherosclerotic risk markers. The reason why MPV was only predictive for the response of prolactinoma may be related to which MPV is a potential marker of platelet reactivity (23) and the half-life of platelets is short; therefore, the marker can be sensitive to measure changes of PRL levels in a shorter time than the other atherosclerotic risk markers. Thus, we think that atherosclerotic risk markers should be regarded when deciding on the cessation of DA therapy in patients with prolactinoma.

Moreover, a new guideline is exclusively necessary for the determination of the optimal duration of DA therapy, and it should be established with a base on the improvement of atherosclerosis in prolactinoma.

Study limitations

Our study did not include a comparison of atherosclerotic risk markers between the group in which relapse of prolactinoma occurred and control subjects. Longitudinal data for healthy patients were not provided because we could not reach the subjects.

Conclusion

Unfavorable cardiovascular risk profiles and high recurrence rates of hyperprolactinemia are still problems for patients with prolactinoma who received CAB therapy and in whom CAB therapy was withdrawn, according to the criteria of recent guidelines. Therefore, new guidelines are necessary for determining the optimal duration of DA therapy. In addition, these guidelines should be established with an aim of improving atherosclerosis in patients with prolactinoma.

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