Hormones and Cancer (2019) 10:45–50
https://doi.org/10.1007/s12672-018-0348-3

ORIGINAL PAPER

Familial Cancer Clustering in Patients with Prolactinoma

Sandra Pekic[1,2] · Ivan Soldatovic[1,3] · Dragana Miljic[1,2] · Marko Stojanovic[1,2] · Mirjana Doknic[1,2] · Milan Petakov[1,2] · Vera Popovic[1]

Received: 18 June 2018 / Accepted: 3 September 2018 / Published online: 8 September 2018

Abstract

People are at higher risk for malignancy as they get older or have a strong family history of cancer. This study aims to collect family history of cancer in a large cohort of patients with pituitary adenomas (PA) in outpatient clinic from years 2005–2017. Overall, 46.6% of 1062 patients with PA had a family member affected with cancer. Breast cancer in family members was reported in 15.3% of patients with prolactinomas which was significantly higher than in families of patients with non-functioning pituitary adenomas (NFPA) (10.0%) or acromegaly (6.8%) ($p = 0.004$). Lung cancer in family members was reported in 12.1% of patients with prolactinomas, significantly higher than in families of NFPA patients (7.0%, $p = 0.049$). Colorectal cancer in relatives of patients with PA was reported with any type of PA. Furthermore, patients with a positive family history of malignancy were diagnosed with PA at an earlier age than patients with a negative family history (43.6 ± 15.9 vs 46.0 ± 16.4 years, $p = 0.015$). Female patients with prolactinoma are more commonly diagnosed before the age of 25 years. Forty-two percent of patients with PA diagnosed before the age of 25 years had a second- and third-degree relative with cancer, significantly higher than patients with PA diagnosed later in life (25.8%, $p < 0.001$). Breast, lung, and colon cancers in second- and third-degree relatives were reported in significantly higher proportion of patients with PA diagnosed before the age of 25 years, compared with patients with PA diagnosed later in life (breast cancer: 10.9 vs 6.1%, $p = 0.033$; lung cancer: 10.9 vs 5.8%, $p = 0.02$; colon cancer: 9.5 vs 4.0%, $p = 0.004$). These results suggest familial cancer clustering in patients with prolactinoma and young patients with PA (younger than 25 years at diagnosis of PA). In particular, there is a strong association between prolactinoma and family history of breast and lung cancers. Further research of possible shared genetic susceptibility of prolactinoma and breast and lung cancers is needed.

Keywords Pituitary adenoma · Prolactinoma · Family history · Cancer · Breast cancer

Introduction

Pituitary adenomas are common benign neoplasms with a prevalence of 1:1000 in the general population. Most have an indolent course (prolonged and stable doubling time) while persistent growth is atypical. Clinically pituitary tumors are classified as functional and non-functional. However, recently, they have been classified into seven subtypes according to their hormone content (somatotroph, lactotroph, thyrotroph, corticotroph, gonadotroph, null cell, plurihormonal, and double adenoma) and not to their secretory status [1]. The majority of pituitary adenomas are sporadic tumors in whom the etiology is still poorly understood. To date the number of molecular genetic factors linked to pituitary tumors accounts for a small proportion (< 5%) of pituitary tumors. Molecular defects responsible for familial pituitary adenoma formation in MEN1, Carney complex, FIPA, and GNAS 1 have been defined [2].

With emphasis on gene testing in several familial cancers (breast, colorectal), other cancers with poorly defined genetics (lung, prostate, bladder cancers, and non-Hodgkin lymphoma) are not considered as familial cancer risk group. Thus, there is a concern that the readily available information of family history remains unused. A recent Swedish study using family history information showed that the cancer risk if a family member is affected is twofold compared to the risk in individuals with unaffected relatives [3]. Authors conclude that

✉ Vera Popovic
popver@gmail.com

[1] School of Medicine, University of Belgrade, Dr Subotic 8, Belgrade 11000, Serbia

[2] Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center Belgrade, Belgrade, Serbia

[3] Institute of Medical Statistics and Informatics, Belgrade, Serbia

familial risk is a shared feature of all cancers and that family history of malignancy deserves more attention in oncology clinics.

During years of clinical practice in endocrinology, we noticed familial clustering of breast cancer in families of our patients with prolactin secreting adenomas (prolactinoma). This observation prompted us to prospectively collect data on family history of malignancy in patients with pituitary adenomas. We examined if there was an association between a specific tumor type in the family and the occurrence of pituitary adenoma in a family member.

Patients and Methods

The patients with pituitary adenoma (acromegaly, prolactinoma, and non-functioning pituitary adenoma) were identified in the out-patient Clinic for Endocrinology, Diabetes and Diseases of Metabolism, University Clinical Center, Belgrade, during the period 2005–2017. The patient population is regarded as unselected. We prospectively collected the demographic data (date of birth, gender), type of pituitary adenoma, diagnosis of hypopituitarism and family history of malignancy. Information of family history was collected on all first-degree relatives (including parents, children, or siblings of the patient) and second- and third-degree relatives (including grandparents, grandchildren, uncles, aunts, first-degree cousins or second-degree cousins of the patient). All the patients were interviewed about their family history by two of the study coauthors belonging to the same team (SP and VP) and applying the same interview protocol. They started with the general question: "Did you have a family member with a cancer?" Then, they asked more specifically about the family history of malignancy: "Did your mother or father, brother or sister have a cancer? Did more distant family member have cancer, your grandmother, grandfather, their children?" When the answer was positive, the investigators asked for more details about the type of cancer in the family. The patients had enough time to recall their family's cancer history. Patients were encouraged to report family history to the best of their knowledge but also to investigate further and any additional information provided by the patient or his/her relatives during the course of the treatment and follow-up was added to the data base. The reproducibility of the answers on family cancer history was tested on the patient's follow-up visits. Same questions were asked again and we collected the data from all visits to our clinic during the whole follow-up period (2005–2017). Some patients reported that a family member was diagnosed with cancer during this long follow-up period. The accompanying family members of the patient with PA, if present, were asked about the data on family cancer history, to add more information or confirm the information provided by the patient.

Statistical Analysis

Results are presented as count (%), means ± standard deviation depending on data type and distribution. Groups are compared using parametric (t test, ANOVA) and nonparametric (Pearson chi-square, Ficher's exact) tests. Overall significant differences were further analyzed using post-hoc testing with Benjamini-Hochberg procedure for p value adjustment. All p values less than 0.05 were considered significant. All data was analyzed using SPSS 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.)

Results

We analyzed data for familial risk for cancers in 1062 patients with pituitary adenoma (PA): 220 patients with acromegaly, 372 patients with prolactinoma and 470 patients with non-functioning pituitary adenoma (NFPA). Twelve patients (1.1%) had MEN 1, one patient had McCune-Albright syndrome and none had Carney complex. Clinical characteristics of these patients are shown in Table 1. In our study, 495 (46.6%) of patients with pituitary adenoma had a family history of cancer, 272 (25.6%) first-degree relatives were affected, and 298 (28.1%) second- and third-degree relatives. In 74 (7.0%) patients, both first-degree and second- and third-degree relatives were affected, while in 165 (15.6%) multiple affected relatives were reported. Types of cancers in families of patients with pituitary adenomas are shown in Table 2. The most prevalent were breast cancer ($n = 119$; 24.0% of all familial malignancies), lung cancer ($n = 101$; 20.4%), and colorectal cancer ($n = 81$; 16.4%) (Table 2).

Clinical characteristics of PA patients with positive or negative family history of cancer are presented in Table 3. Female sex was more prevalent in PA patients with positive family cancer history (66.9%), compared with PA patients with negative family cancer history (60.8%, $p = 0.042$, Table 3). The PA patients with positive family cancer history were younger at diagnosis of PA in comparison with PA patients with negative family cancer history (43.6 ± 15.9 vs 46.0 ± 16.4 years, $p = 0.015$). There were no differences in hypopituitarism or PA type between patients with positive and negative familial cancer history (Table 3).

Overall, there was a borderline difference of positive familial cancer history in patients with different types of pituitary adenoma ($p = 0.056$, Table 1). Fifty-one percent (51.6%) of prolactinoma patients had a positive family cancer history, compared with NFPA patients (44.0%) and patients with acromegaly (43.6%; Table 1). The association of positive familial cancer history and specific pituitary adenoma type was more pronounced in second- and third-degree relatives ($p = 0.001$), compared with first-degree relatives ($p = 0.011$).

Table 1 Clinical characteristics and history of malignancy in patients with pituitary adenoma and their families

	Acromegaly	Prolactinoma	NFPA	Total	*p* value
N	220	372	470	1062	
Male sex	86 (39.1%)^{p}	96 (25.8%)^{a,n}	204 (43.4%)^{p}	386 (36.3%)	0.001
Age (mean ± SD, years)					
Actual age	54.9 ± 13.5^{p}	41.1 ± 13.8^{a,n}	55.5 ± 16.5^{p}	50.6 ± 16.5	0.001
At diagnosis of PA	47.2 ± 13.6^{p,n}	35.4 ± 13.0^{a,n}	51.2 ± 16.1^{a,p}	44.9 ± 16.2	0.001
Malignancy in the family	96 (43.6%)	192 (51.6%)^{n*}	207 (44.0%)^{p*}	495 (46.6%)	0.056
1° relatives	55 (25.0%)	77 (20.7%)^{n}	140 (29.8%)^{p}	272 (25.6%)	0.011
Parents	41 (18.6%)	66 (17.7.%)^{n*}	110 (23.4%)^{p*}	217 (20.4%)	0.098
Siblings	15 (6.8%)^{p}	11 (3.0%)^{a,n}	34 (7.2%)^{p}	60 (5.6%)	0.020
2&3° relatives	55 (25.0%)^{p}	144 (38.7%)^{a,n}	99 (21.1%)^{p}	298 (28.1%)	0.001
All degrees relatives**	14 (6.4%)	29 (7.8%)	32 (6.8%)	75 (7.1%)	0.673
Breast cancer in 1° rel	4 (1.8%)^{n,p*}	19 (5.1%)^{a}	29 (6.2%)^{a*}	52 (4.9%)	0.046
Lung cancer in 1° rel	9 (4.1%)	9 (2.4%)	16 (3.4%)	34 (3.2%)	0.507
Colon cancer in 1° rel	6 (2.7%)	13 (3.5%)	16 (3.4%)	35 (3.3%)	0.866
Breast cancer in 2&3° rel	12 (5.5%)^{p}	41 (11.0%)^{a,n}	19 (4.0%)^{p}	72 (6.8%)	0.001
Lung cancer in 2&3° rel	14 (6.4%)	37 (9.9%)^{n}	18 (3.8%)^{p}	69 (6.5%)	0.002
Colon cancer in 2&3° rel	5 (2.3%)	21 (5.6%)	25 (5.3%)	51 (4.8%)	0.140

PA pituitary adenoma, *NFPA* nonfunctioning pituitary adenoma, *1°* first-degree relatives, *2&3°* second- and third-degree relatives, *rel* relatives

Single group by group comparisons, with correction ($p < 0.05$): [a] Acromegaly, [p] Prolactinoma, [n] NFPA; [*] Single group by group comparisons, without correction ($p < 0.05$)

[**] Some patients are represented in more than one category if having both a first-degree and second- and third-degree relative with a cancer

In the next step, we analyzed in more details the associations of a specific PA subtype with the type of cancer in the family, especially with the most prevalent familial cancer cases (breast cancer, lung cancer, and colorectal cancer). Fifteen percent (15.3%) of patients with prolactinoma had first-, second-, and third-degree relative with breast cancer, significantly higher than patients with NFPA (10.0%) or acromegaly (6.8%) ($p = 0.004$). Next in order was lung cancer: 12.1% of patients with prolactinoma had a relative in first-, second-, and third-degree with lung cancer, significantly higher than patients with NFPA (7.0%, $p = 0.049$), not different from patients with acromegaly (10.5%, $p = 0.595$). The percentage of patients with specific PA who had a family member with colorectal cancer did not reach significance (8.9% of patients with prolactinoma, 7.9% with NFPA and 5.0% with acromegaly) ($p = 0.222$).

Furthermore, we analyzed the association of a specific PA subtype with the familial cases of cancer in different degree relatives (Table 1). Thirty-nine (38.7%) percent of patients with prolactinoma had second- and third-degree relative with cancer, significantly higher than patients with NFPA (21.1%) or acromegaly (25.0%) ($p = 0.001$). Eleven percent of patients with prolactinoma had second- and third-degree relative with breast cancer, significantly higher than patients with NFPA (4.0%) or acromegaly (5.5%) ($p = 0.001$, Table 1). Next in order was lung cancer: 9.9% of patients with prolactinoma had a relative in second- and third-degree with lung cancer, significantly higher than patients with NFPA (3.8%) or acromegaly (6.4%) ($p = 0.002$, Table 1).

Clinical characteristics and familial history of malignancy in patients with PA diagnosed prior 25 and after 26 years of age are presented in Table 4. Female patients with prolactinoma predominate in younger group of patients. Fifty percent (50.3%) of patients with PA diagnosed prior 25 years of age had a positive family cancer history (Table 4). Forty-two percent (42.2%) of patients with PA diagnosed before the age of 25 had a second- and third-degree relative with cancer, significantly higher than patients with PA diagnosed after the age of 26 (25.8%, $p < 0.001$, Table 4). Breast, lung, and colon cancers in second- and third-degree relatives were reported in significantly more patients with PA diagnosed before the age of 25, compared with patients with PA diagnosed after the age of 26 (breast cancer: 10.9 vs 6.1%, $p = 0.033$; lung cancer: 10.9 vs 5.8%, $p = 0.02$; colon cancer: 9.5 vs 4.0%, $p = 0.004$, Table 4).

Discussion

Findings from our study suggest that 46.6% of patients with pituitary adenoma of any type have a family history of malignancy. In our series, among tumors that associated with

Table 2 Type of malignancy in families of patients with pituitary adenoma

	Acromegaly *n*	Prolactinoma *n*	NFPA *n*	Total *n*
Breast	15	57	47	119
Lung	23	45	33	101
Colorectal	11	33	37	81
PVU + endometrial	9 + 2	20 + 1	25 + 3	60
Gastric Ca	8	14	15	37
Prostate	10	13	12	35
Upper erodigestive tract	9	10	14	33
Brain	5	11	14	30
Leukemia	8	4	10	22
Pancreas	3	8	4	15
Liver	1	7	8	16
Lymphoma	4	3	8	15
Bone	1	6	7	14
Kidney/ureter	3	6	6	15
Urinary bladder	4	4	6	14
Melanoma	1	6	4	11
Thyroid gland	3	4	2	9
Ovary	2	-	7	9
Testicular Ca	2	3	3	8
Skin Ca	-	2	2	4
Multiple myeloma	-	1	1	2
Duodenal Ca	-	-	2	2
Neuroendocrine	-	2	-	2
Paranasal sinus	-	-	1	1
Unknown localization	4	7	7	18

NFPA nonfunctioning pituitary adenoma

prolactinomas in families, breast and lung cancers were the most prominent. In a study based on the Swedish Family-Cancer Database, among tumors that associated with pituitary adenoma in families, breast cancer was also prominent [4]. Colorectal cancer was associated with all types of pituitary adenoma and not with a specific PA subtype.

Another interesting observation in our study is that patients with positive family cancer history were younger at diagnosis of pituitary adenoma, which confirms the findings in the mentioned Swedish study that early onset pituitary tumors in offspring were associated with parental leukemia, and pituitary tumors diagnosed at ages 30–45 years were in excess in offspring whose mothers were diagnosed with breast cancer [4]. We noticed that patients with PA diagnosed at younger age (before the age of 25) had more family members with breast, lung, and colon cancer cases in the second- and third-degree relatives, compared with patients with PA diagnosed later in life. Beside younger age in of patients with positive family cancer history, female sex was also more prevalent in these patients, compared with PA patients with negative family cancer history. These data are in accordance with the finding that patients with prolactinoma (who had more family cancer cases) are predominantly females and on average are younger compared with patients with other PA types.

There are only few epidemiological studies supporting our clinical observation of familial cancer clustering in patients with pituitary adenoma, which assessed the presence of associated malignant tumors in families presenting pituitary adenomas [4, 5]. The already mentioned Swedish study based on nationwide Swedish Family-Cancer Database on 10.5 million individuals containing families with parents and offspring [4] included 3239 pituitary tumor patients. The results of that study suggested an association of pituitary adenomas with some cancers in the family (skin cancer, leukemia, nervous system hemangiopericytomas, breast, and colorectal cancer) [4]. The second study analyzed the Utah Population Database with genealogical data from Utah pioneers and their descendents with more than 7.5 million individuals [5]. The analysis of this database showed a significant excess of several cancers (prostate and other cancer sites) among first-, second-, and third-degree relatives of the 575 patients with pituitary adenoma. These epidemiological observations were explained by shared genetics and/or environmental influences, with a note

Table 3 Clinical characteristics of pituitary adenoma patients with positive or negative family cancer history

	Positive family cancer history	Negative family cancer history	*p* value
N	495 (46.6%)	567 (53.4%)	
Male sex	164 (33.1%)	222 (39.2%)	0.042
Age (yrs.)			
Actual age	49.1 ± 16.1	51.9 ± 16.6	0.009
At diagnosis of PA	43.6 ± 15.9	46.0 ± 16.4	0.015
Type of PA			
Acromegaly	96 (19.4%)	124 (21.9%)	0.056
Prolactinoma	192 (38.8%)	180 (31.7%)	
NFPA	207 (41.8%)	263 (46.4%)	
Hypopituitarism	114 (23.0%)	154 (27.2%)	0.174

PA pituitary adenoma, *NFPA* nonfunctioning pituitary adenoma

*Results are presented as counts (%, where appropriate), or mean ± standard deviation

that common environmental factors cannot explain the excess of malignancies in distant relatives.

Our study is a prospective study with some limitations, such as the reliance on self-reporting of the family history of cancer and the fact that a family history of cancer was assessed at baseline. However, eventual changes in family cancer history were captured during follow-up as much as possible. Data suggest that patient-reported family cancer histories are generally accurate and valuable [3, 6]. Also, there may be biases in the way that different patients report family cancers, depending on the PA patient's sex and age. Perhaps female PA patients are more likely than males to recall a breast cancer in a more distant relative, or younger PA patients may be more likely to report a cancer in grandparents if they are still alive

Table 4 Clinical characteristics and history of malignancy in patients with pituitary adenoma diagnosed prior 25 years of age and after 26 years of age

	PA diagnosed prior 25 years of age	PA diagnosed after 26 years of age	*p* value
N	147 (13.8%)	915 (86.2%)	
Male sex	31 (21.1%)	355 (38.8%)	< 0.001[a]
Age (yrs.)			
Actual age	27.3 ± 8.4	54..4 ± 14.2	< 0.001[b]
At diagnosis of PA	21.3 ± 3.0	48.7 ± 14.1	< 0.001[b]
Type of PA			
Acromegaly	14 (9.5%)	206 (22.5%)	< 0.001[a]
Prolactinoma	96 (65.3%)	276 (30.2%)	
NFPA	37 (25.2%)	433 (47.3%)	
Hypopituitarism	15 (10.2%)	253 (27.7%)	< 0.001[a]
Positive family history of Mg	74 (50.3%)	421 (46.0%)	0.329 [a]
1° relatives	16 (10.9%)	256 (28.0%)	< 0.001[a]
2&3° relatives	62 (42.2%)	236 (25.8%)	< 0.001[a]
Breast cancer in 1° rel	8 (5.4%)	44 (4.8%)	0.741[a]
Breast cancer in 2&3° rel	16 (10.9%)	56 (6.1%)	0.033 [a]
Lung cancer in 1° rel	1 (0.7%)	33 (3.6%)	0.074[c]
Lung cancer in 2&3° rel	16 (10.9%)	53 (5.8%)	0.020 [a]
Colon cancer in 1° rel	1 (0.7%)	12 (1.3%)	0.076 [c]
Colon cancer in 2&3° rel	14 (9.5%)	37 (4.0%)	0.004 [a]

*Results are presented as counts (%). or mean ± standard deviation

PA pituitary adenoma, *Mg* malignancy, *NFPA* nonfunctioning pituitary adenoma, *1°* first-degree relatives, *2&3°* second- and third-degree relatives

[a] Pearson chi-square test

[b] *t* test

[c] Fisher's exact test

at the time they reported it, so such a report might be more common in younger PA patients. We did not have possibility to correlate the recollected report and the incidence of true cancers in family members from medically verified cancer cases in the Serbian Cancer Registry. However, we believe that patient interview as an inexpensive and available method of assessing family history provides valuable hypothesis on associations which may with further research shed light on pituitary tumorigenesis which still remains unknown. Possible cross-cultural differences in fidelity of self-reporting family history may also exist. We believe that in the cultures of Southeast Europe where this study was performed, close and open communication within wider family circles, and a culture of openly volunteering information on personal and family health may provide more reliability to the use of the interview as a method of assessment of family history of cancer.

A further research directed to investigate a possible shared genetic susceptibility of prolactinoma and breast and lung cancers would provide more definitive interpretation of the associations observed in our cohort of patients with pituitary adenoma.

In conclusion, in the absence of genetic background for most common cancers and pituitary adenomas, family history of malignancy is a readily available tool for screening and prevention strategies in patients with pituitary adenomas.

Funding This study was supported by a grant from the Ministry of Science of Republic of Serbia (Project 175033).

Compliance with Ethical Standards

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

References

1. Osamura RY, Lopes MBS, Grossman A, Kontogeorgos G, Trouillas J (2017) Introduction. In: Lloyd RV, Osamura RY, Kloppel G, Rosai J (eds) WHO classification of tumours of endocrine organs, 4th edn. IARC Press, Lyon
2. Marques P, Korbonits M (2017) Genetic aspects of pituitary adenomas. Endocrinol Metab Clin N Am 46:335–374
3. Frank C, Fallah M, Sundquist J, Hemminki A, Hemminki K (2015) Population landscape of familial cancer. Sci Rep 5:12891
4. Hemminki K, Forsti A, Ji J (2007) Incidence and familial risks in pituitary adenoma and associated tumors. Endocr Relat Cancer 14: 103–109
5. Couldwell WT, Cannon-Albright LS (2014) Co-prevalence of other tumors in patients harboring pituitary tumors. J Neurosurg 121: 1474–1477
6. Murff HJ, Spigel DR, Syngal S (2004) Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. JAMA 292:1480–1489