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ORIGINAL ARTICLE

Is there any gender difference in epidemiology, clinical presentation and co-morbidities of non-functioning pituitary adenomas? A prospective survey of a National Referral Center and review of the literature

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Abstract

Purpose Gender differences in patients diagnosed with non-functioning Pituitary Adenomas (NFPA) in a National Referral Center for Pituitary Tumors at the Federico II University of Naples, Italy.

Methods Patients newly diagnosed with non-functioning sellar masses found on pituitary Magnetic Resonance Imaging from January 1st 2016 to December 31th 2018 underwent anthropometric measurements, basal evaluation of pituitary function, and metabolic assessment. Fatty live index (FLI) and visceral adiposity index (VAI) were calculated.

Results Seventy-three patients (35 males, 51.1 ± 17.0 years; 38 females, 41.8 ± 18.1 years) presented with NFPA. Lesions > 1 cm (85.7% vs. 47.3%; $\chi^2 = 10.26$, $p = 0.001$) and hypopituitarism (77.1% vs. 7.9%; $\chi^2 = 33.29$, $p = 0.001$) were more frequent in males than females. The highest sizes of pituitary adenomas were significantly associated with male gender (OR = 1.05, $p = 0.049$; $R^2 = 0.060$; IC 1.00–1.10). Headache (62.8% vs. 31.6%; $\chi^2 = 5.96$, $p = 0.015$) and visual field deficits (57.1% vs. 26.3%; $\chi^2 = 5.93$, $p = 0.015$) were significantly more frequent in males than in females. There was no sex difference in obesity prevalence, but the metabolic syndrome was more common among males than females (60.6% vs. 26.3%; $\chi^2 = 7.14$, $p = 0.001$). FLI was also higher in males (69.6 ± 27.3 vs. 49.2 ± 31.3; $p < 0.001$), while there were no differences in VAI.

Conclusions Apart from the possible delay in the diagnosis induced by the gender differences in symptom presentation, the higher prevalence of macroadenomas amongst NFPA in males compared with females let to hypothesize a key role of the sex hormone profile as predictive factors of their biological behavior and metabolic profile. Further studies are, however, mandatory to better support the influence of gender differences on onset, progression, and metabolic consequences of NFPA.

Keywords NFPA · Gender differences · Tumor size · Hypopituitarism · Metabolic syndrome · Cardio-metabolic indices

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Introduction

The pituitary gland, the sella turcica, and the parasellar region can be affected by a wide variety of lesions, including benign and malignant neoplasms, such as anterior and posterior pituitary tumors, parasellar tumors, such as craniopharyngiomas (3–5% of all intracranial expanding lesions in adult, 6% during the pediatric age), as well as non-neoplastic tumor-like lesions and dysembryogenetic lesions, such as Rathke's pouch cyst [1]. Non-functioning pituitary adenomas (NFPA) are among the most common subtype of tumors that arise from the adenohypophysis, accounting for up to 54% of pituitary adenomas [2]. NFPA represent usually benign and slow-growing neoplasms, without clinical or biochemical evidence of hormone overproduction, except for a mild hyperprolactinemia in a number of cases [3, 4]. Although NFPA are not infrequently found incidentally as pituitary microadenomas (< 1 cm) and are usually of no clinical relevance, they are commonly macroadenomas and diagnosed because of hypopituitarism and/or mass effect, with compressive symptoms, including headache and visual field defects, as a consequence of their suprasellar growth [4, 5]. Roughly, 70% of patients with non-functioning macroadenoma present visual impairments upon diagnosis and most patients have Growth Hormone (GH) deficiency and hypogonadism [4, 5]. In addition, most NFPA express different pituitary hormones or their transcription factors with immunohistochemistry, mainly gonadotropins or their subunits, and are termed silent pituitary adenomas (SPA) [3]. SPA do not secrete hormones at a clinically relevant level, however their pre-operative identification determines the postoperative medical therapy [6, 7]. The clinical course of NFPA might be difficult to predict. Indeed, in some cases NFPA exhibit an aggressive course, with local invasion and compression of surrounding tissues, rapid tumor growth, and resistance to standard therapies. In addition, the absence of clinical symptoms of hormonal hypersecretion is largely responsible for a delay in diagnosis, with serious consequences on the clinical course. Currently, there is still limited information on markers or molecular alterations responsible for the aggressive behavior of NFPA [8, 9]. Gender is an important non-modifiable risk factor for the development of a variety of cancers [10]. There is a trend toward a gender-related difference in surgical outcome, clinical presentation, duration of symptoms, tumor size, tumor histology, and restoration of normal pituitary function in patients who are surgically treated and histologically proven pituitary tumors. However, there are still few data in literature, which support this information [11]. Unlike functioning pituitary adenomas [12], data on gender differences in NFPA are still conflicting and up to now there are no detailed data on an Italian series. In addition, data on gender differences in anthropometric measurements and metabolic profile in NFPA are still lacking.

Aim of this prospective study was to explore the presence of gender differences based on anthropometric, clinical, biochemical, endocrine-metabolic and instrumental characteristics of patients newly diagnosed with non-functioning sellar masses found on pituitary Magnetic Resonance Imaging (MRI) on a three years period (2016–2018) in a National Referral Center for Pituitary Tumors at the Federico II University of Naples, Italy.

Patients and methods

Study design

This is a prospective survey study.

Inclusion criteria

Inclusion criteria were: (1) patients diagnosed with sellar/extrasellar masses found on MRI; (2) absence of pituitary hormone excess.

Patients

From January 1st 2016 to December 31th 2018, 281 consecutive patients newly diagnosed with sellar/extrasellar masses from the same geographical area around Naples metropolitan area in Campania region, Italy, were admitted to National Referral Center for Pituitary Tumors at the Federico II University of Naples. Patients with NFPA (35 males, 51.1 ± 17.0 years; 38 females, 41.8 ± 18.1 years) were included in this study after their written informed consent had been obtained. Since 1997, all patients admitted to the Neuroendocrine Unit of the Federico II University in Naples sign a written consent for the scientific use of their data. When patients are aged below 18 years, the parents of the legal representatives sign the permission on their behalf. The study design was made in accordance with the Helsinki II Declaration for Study on human experimentation and approved by the local ethic committee (n. 63/97).

Study protocol

At study entry the following parameters were evaluated in all patients:

Clinical evaluation

Anthropometric measurements were performed between 8 and 10 a.m. The measurements were made in a standard way

by the same operator (a nutritionist experienced in providing nutritional assessment and body composition), with subjects wearing only light clothes and without shoes, as previously reported [13, 14]. In each subject, weight and height were measured to calculate the BMI (kg/m^2). Height was measured to the nearest 0.5 cm using a wall-mounted stadiometer (Seca 711; Seca, Hamburg, Germany). Body weight was determined to the nearest 0.1 kg using a calibrated balance beam scale (Seca; Seca, Hamburg, Germany). BMI was classified according to the World Health Organization (WHO)'s criteria, with normal weight: 18.5–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; obesity, > 30.0 kg/m^2 [15]. Waist circumference was measured to the closest 0.1 cm using a non-stretchable measuring tape at a midway level between the lower edge of the rib cage and the iliac crest [16].

In all subjects Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were measured three times, two min apart, with a random zero sphygmomanometer (Gelman Hawksley Ltd., Sussex, UK) after the subjects had been sitting for at least 10 min. In the analysis, we used the average of the two measurements. For patients treated with antihypertensive drugs were considered to be the blood pressure pre-treatment.

The presence of metabolic syndrome was assessed according to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III definition, metabolic syndrome is present if three or more of the following five criteria are met: waist circumference ≥ 102 cm (men) or 88 cm (women), blood pressure ≥ 130/85 mmHg, fasting triglycerides level ≥ 150 mg/dl, fasting HDL cholesterol level ≤ 40 mg/dl (men) or ≤ 50 mg/dl (women), and fasting glucose ≥ 100 mg/dl or a diagnosis of type 2 diabetes mellitus [17].

Biochemical evaluation

Hypopituitarism was diagnosed clinically based on clinical manifestations, basal evaluation of pituitary function, and provocative tests, according to Endocrine Society Clinical Practice Guidelines [18]. In detail, GH response after GHRH + arginine was classified, according to BMI-specific cutoffs, as deficient when GH peak was ≤ 4.2 ng/ml in subjects with BMI > 30 kg/m^2 and < 9 ng/ml in subjects with BMI < 29.9 kg/m^2 [19, 20]; glucocorticoid deficiency was defined by basal serum cortisol values < 3 µg/dl or by 1 µg corticotrophin-stimulated cortisol < 18 µg/dl. Hypothyroidism was defined by serum free thyroxine below the reference ranges. In men, hypogonadism was diagnosed by measuring morning total testosterone levels; in those patients in whom total testosterone concentrations were near the lower limit of the normal range, sex hormone binding protein was measured for calculating the bioavailable testosterone. In women, hypogonadism was defined by irregular or absent menstrual cycles. Patients with diagnosis of hypogonadism under chronic replacement treatment with sex steroids were considered eugonadal. The degree of hypopituitarism was defined by the involvement of one or more axes. In the first degree of we have grouped patients with hypopituitarism involving < 3 axes, in the second degree patients with hypopituitarism involving ≥ 3 axes.

Assays

Samples were collected in the morning between 8 and 10 a.m., after an overnight fast of at least 8 h and stored at − 80 °C until being processed. All biochemical analyses including fasting plasma glucose, total cholesterol, fasting plasma triglycerides, Alanine Transaminase (ALT), Aspartate Aminotransferase (AST), and γ-Glutamyltransferase (γGT) were performed with a Roche Modular Analytics System in the Central Biochemistry Laboratory of our Institution. Low-Density Lipoprotein (LDL) cholesterol and HDL cholesterol were determined by a direct method (homogeneous enzymatic assay for the direct quantitative determination of LDL and HDL cholesterol); as previously reported [21–23].

Serum GH levels were measured by immunoradiometric assay (IRMA) using commercially available kits (HGH-CTK-IRMA, Sorin, Saluggia, Italy). Serum IGF-1 levels were measured by IRMA after ethanol extraction (DSL Inc., Webster, TX, USA). TSH, FSH, LH, ACTH serum and urinary cortisol and PRL were assayed using commercially available kits (Immunolite Diagnostic Products Co., Los Angeles, CA, USA).

Cardio-metabolic indices

VAI score has been calculated by the following sex-specific formula, with TG levels expressed in mmol/L and HDL levels expressed in mmol/l:

$$\text{Males: } \text{VAI} = [\text{WC}/39.68 + (1.88 \times \text{BMI})] \times (\text{TG}/1.03) \times (1.31/\text{HDL})$$

$$\text{Females: } \text{VAI} = \left[\text{WC}/36.58 + (1.89 \times \text{BMI})\right] \times (\text{TG}/0.81) \times (1.52/\text{HDL})$$

Age-specific VAI cut-off values were used according to Amato et al. [24, 25]

FLI was calculated with the formula:

$$\left[\mathrm{FLI} = \mathrm{eL}/(1+\mathrm{eL}) \times 100,\ L = 0.953 \times \log_e \text{triglycerides} + 0.139 \times \mathrm{BMI} + 0.718 \times \log^e \gamma GT + 0.053 \times \mathrm{WC} - 15.745\right]$$

A score of 30 was considered as the cut-off value based on Bedogni's criterion [26].

Instrumental evaluation

Tumor mass was evaluated by MRI. MRI studies were performed on clinical 0.5 T and 1 T scanners, using T1 weighted gradient recalled-echo (repetition time 200–300 ms; echo time10–12 ms; flip angle 90 8, 4 signal averages) in the sagittal and coronal planes. The acquisitions were repeated before and after the administration of 0.1 mmol gadolinium chelate. In all patients with macroadenomas and pituitary lesions > 1 cm, the assessment of visual field defects, by Goldmann–Friedmann perimetry, and visual acuity were performed at baseline and during the follow up. The distinction between microadenoma (maximal diameter below 10 mm) and macroadenoma (maximal diameter equal or above 10 mm) was obtained by measuring the maximum transverse diameter of the adenoma on the coronal plane.

Statistical analysis

Quantitative variables that conformed to the normal distribution were reported as mean ± SD. Comparison among groups according to gender was as follows: Quantitative variables were compared with Student *t* test for unpaired data. Qualitative parameters (tumor characteristics, degrees of hypopituitarism, presence/absence metabolic syndrome) were reported as percentage (%) and compared with χ^2 test. Proportional odds ratio (OR) models, 95% interval confidence (IC), and R^2, were performed to assess the association among gender and size of the pituitary adenomas. We established the level of statistical significance as $p < 0.05$. All statistical analyses were performed using SPSS Statistics for Windows, Version 22.0.

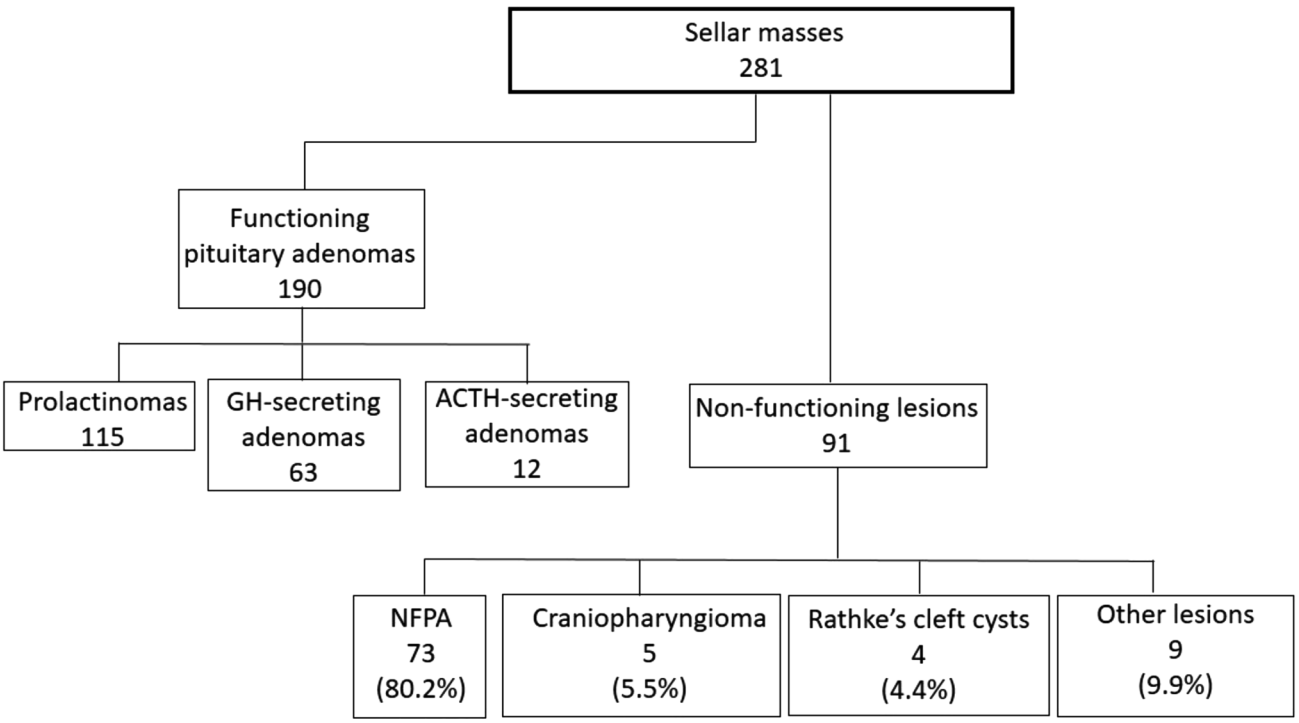

Fig. 1 Patients with sellar masses on a three years period (2016–2018) affering to the National Referral Center for Pituitary Tumors at the Federico II University of Naples, Italy

Table 1 Distribution by gender of 91 non-functioning lesions at study entry

	Total (%)	Males (%)	Females (%)	*p* values
NFPA	80.2	87	75	0.24
Craniopharyngiomas	5.5	7.7	4	0.76
Rathke's pouch cysts	4.4	0	4.3	/
Other lesions: Astrocytoma (3); Chondrosarcoma (1) Medulloblastoma (1); Sinus cavernous meningioma (1); Psammomatous meningioma (1) Germinoma (1); Chordoma (1)	9.9	5	13.4	0.35

p = significance males *vs.* females

During the study period, NFPA represented the vast majority of all patients with non-functioning lesions. Rathke's pouch cysts (4.4%) were seen exclusively in females, while no statistically significant gender differences were found among other sellar and/or parasellar mass. *NFPA:* Non-functioning pituitary tumors.

Results

Epidemiology

During the study period, among 281 sellar masses 190 (67.6%) were pituitary adenomas, while 91 (32.4%) were non-functioning lesions. In particular, among functioning pituitary adenomas 115 were prolactinomas, 63 GH-secreting adenomas and 12 ACTH-secreting adenomas (Fig. 1). Among non-functioning lesions, NFPA were 80.2% (73 pts.), 5.5% (5 pts.) presented with craniopharyngiomas, 4.4% (4 pts.) with Rathke's pouch cysts, and 9.9% (9 pts.) with other lesions (Fig. 1). Sex-distribution of patients with non-functioning pituitary tumors included in this study were shown in Table 1. Rathke's pouch cysts were seen exclusively in females, while no statistically significant gender differences were found among other pituitary lesions. Anthropometric and clinical variables and tumor characteristics of 73 patients with NFPA by gender were shown in Table 2. As expected, the waist circumference was larger in males compared with females.

Tumor size

Pituitary macroadenomas (> 1 cm) were significantly more frequent in males than in females (85.7% vs. 47.3%; $\chi^2 = 10.26$, $p = 0.001$). The size of the pituitary lesions was significantly higher in males than in females (19.1 mm ± 8.5 vs. 14.8 mm ± 10.4; $p = 0.044$) (Table 2). The highest sizes of pituitary adenomas were significantly associated with male gender (OR = 1.05, $p = 0.049$; $R^2 = 0.060$; IC 1.00–1.10). In particular, 34 lesions were incidentally discovered (46.6%), and among them 23 lesions were diagnosed in women (67.7%) and 11 in men (38.5%) ($\chi^2 = 5.09$, $p = 0.024$).

Pituitary function

Hypopituitarism was significantly more common among males than females (77.1% vs. 7.9%; $\chi^2 = 33.29$, $p < 0.001$). In particular, while there were no differences between both sexes in hypopituitarism involving < 3 axes (first degree) (Table 2), males showed ≥ 3 axes involved (second degree) more frequently than females (Table 2). Diabetes insipidus was present in only four males, and deficits in the somatotropic, thyrotropic, corticotropic, and gonadotropic axes were more frequent in males than females. Among patients with hypopituitarism, 17 males (48.6%) and 9 females (23.7%) received replacement therapy with *l*-thyroxine ($\chi^2 = 3.89$, $p = 0.048$), while 21 males (60.0%) and 11 females (28.9%) were treated with cortisone acetate ($\chi^2 = 5.93$, $p = 0.015$). No differences were found between males and females about doses of *l*-thyroxine (69.2 ± 27.9 µg/day vs. 63.6 ± 33.7 µg/day, respectively; $p = 0.649$) and cortisone acetate (26.5 ± 12.3 mg/day vs. 20.5 ± 9.3 mg/day, respectively; p = 0.166). Eight males were treated with testosterone enanthate (250 mg IM/month), and three premenopausal females were treated with oral estroprogestins. Among postmenopausal women (11 patients), none of them were treated with hormonal replacement therapy. Finally, in only male patients, therapy with rhGH (0.2–0.3 mg/day subcutaneously; four patients), and desmopressin (5–20 µg/day intranasally; four patients) was required.

Compressive symptoms

Overall data suggested that the presence of headache (62.8% *vs.* 31.6%; $\chi^2 = 5.96$, $p = 0.015$) and visual field deficits (57.1% vs. 26.3%; $\chi^2 = 5.93$, $p = 0.015$) were more frequently observed in males than in females.

Table 2 Anthropometric and clinical variables and tumor characteristics of 73 patients with NFPA by gender at study entry

	Males	Females	*p* values
No	35	38	
Anthropometric characteristics			
Age (years)	51.1 ± 17.0	41.8 ± 18.1	**0.028**
BMI (kg/m^2)	28.3 ± 4.5	25.9 ± 4.6	**0.027**
Waist circumference (cm)	97.1 ± 11.4	88.7 ± 11.6	**< 0.001**
Hip circumference (cm)	95.8 ± 13.9	95.6 ± 10.1	0.923
Ratio	1.1 ± 0.1	0.9 ± 0.1	**< 0.001**
Tumor characteristics			
Macroadenomas	85.7.%	47.3%	**0.001**
Tumor size (cm)	19.3 ± 8.8	14.3 ± 11.1	**0.035**
Hypopituitarism degree			
0 (no pituitary axis deficit)	22.9%	55.3%	**0.009**
1 (< 3 axis deficits)	48.6%	44.7%	**< 0.001**
2 (≥ 3 axis deficits)	28.6%	0	/
Diabetes insipidus	11.4%	0	/
Pituitary deficit			
GH	11.4%	2.6.%	0.306
TSH	42.9%	10.5%	**0.004**
ACTH	62.9%	31.6%	**0.015**
FSH/LH	31.4%	10.5%	0.055
Compressive symptoms			
Headache	62.8%	31.6%	**0.015**
Visual field defects	57.1%	26.3%	**0.015**
Replacement therapy			
l-thyroxine	48.6%	23.7%	**0.048**
Cortisone acetate	60.0%	28.9%	**0.015**
rhGH	11.4%	0%	/
TRT	22.9%		/
HRT		7.9%	/
Desmopressin	11.4%	0%	/
Dose of replacement therapy			
l-thyroxine (μg/day)	69.2 ± 27.9	63.6 ± 33.7	0.649
Cortisone acetate (mg/day)	26.5 ± 12.3	20.5 ± 9.3	0.166

Significant *p* values are been reported in bold

Values are expressed as (mean ± SD). Significant differences between males and females are noted (Student's *t* test for unpaired data and and χ^2 test)

rhGH recombinant human growth hormone, *THT* testosterone replacement therapy, *HRT* hormonal replacement therapy

Endocrine-metabolic characteristics

Among hormonal profile, besides the expected differences in gonadotropins levels between postmenopausal females and males, serum FT4 and cortisol levels, and free urinary cortisol were lower in males than females (Table 3).

Twenty-one patients presented with obesity (28.8%), but there was no sex difference in obesity prevalence (28.7% males *vs* 36.8% females; $\chi^2 = 1.77$, $p = 0.183$). Gender differences were however evidenced in HDL cholesterol (47.6 ± 8.4 *vs.* 53.3 ± 8.4; $p = 0.001$) and triglycerides levels (188.6 ± 42.2 vs. 157.9 ± 42.9; $p = 0.004$). The prevalence of the metabolic syndrome was more common among males than females (60.6% vs. 26.3%; $\chi^2 = 7.14$, $p = 0.001$). FLI was also higher in males than in females (69.6 ± 27.3 vs. 49.2 ± 31.3; $p < 0.001$), while there were no differences in VAI (Table 3).

Discussion

Patients with non-functioning sellar masses, in particular NFPA, tend to have no specific symptoms and are generally discovered at an older age than functioning pituitary adenomas. Thus, often the diagnosis and the treatment of non-functioning sellar masses might be challenging [2–5]. In this prospective, cohort study performed in a single National Referral Center for Pituitary Diseases in a three-year period we found that among sellar masses 67.6% were pituitary adenomas, while 32.4% were non-functioning lesions, which were represented in the vast majority of cases by NFPA. This result was in line with data from different population samples reporting that approximately 90% of sellar mass in adults are pituitary adenomas [27] and NFPA represented among 14–54% of pituitary adenomas [2].

NFPA are the most common type of pituitary adenomas among macroadenomas, and are mainly silent gonadotroph adenomas with rarely occurring other anterior pituitary hormones-secreting adenomas, such as silent somatotropinomas [6, 7], while prolactinomas are more common among both micro and macroadenomas [3, 28]. Accordingly, data from a large national Italian survey involving 37 centers and recording a total of 1.479 neurosurgical procedures for hypothalamic/pituitary tumors evidenced a quite similar histotype distribution of their cases, where 81% were pituitary adenomas, with a consistently lower prevalence of Rathke's cleft cyst (4%) and craniopharyngioma (9%) [29]. In this Italian series, however, data on tumors characteristics and clinical presentation by gender were not evaluated. Conversely, Daly et al. [30] showed that the prevalence of NFPA was 14.7% of all pituitary adenomas, but these Authors included in their study only pituitary tumors.

This is the first study in an Italian series aimed to investigate the gender differences in tumor characteristics, clinical and metabolic presentation of non-functioning sellar masses. Gender is an important, non-modifiable risk factor for the development of a variety of cancers [10]. There is a clear gender difference in the prevalence of functioning pituitary adenomas and their clinical presentation, especially considering prolactinomas that in men could have an aggressive course [12, 31]. Contrariwise, data about gender

Table 3 Biochemical and endocrine profile of 73 patients with NFPA by gender at study entry

	Males	Females	*p* values	Normal range
No	35 patients	38 patients		
BUN (mg/dl)	37.3 ± 15.4	30.1 ± 7.9	**0.014**	21–43
Creatinine (mg/dl)	0.97 ± 0.23	0.87 ± 0.28	0.069	0.7–1.3
Blood glucose (mg/dl)	94.2 ± 12.5	88.1 ± 12.5	0.061	70–110
Total Cholesterol (mg/dl)	208.5 ± 38.3	202.6 ± 47.6	0.557	< 190
HDL Cholesterol (mg/dl)	47.6 ± 8.4	53.3 ± 8.4	**0.001**	> 40/ > 50
LDL Cholesterol (mg/dl)	124.2 ± 39.3	117.7 ± 47.9	0.527	< 115 mg/dl
Triglycerides (mg/dl)	188.6 ± 42.2	157.9 ± 42.9	**0.004**	< 150 mg/dl
Metabolic syndrome (%)	60.0%	26.3%	**0.001**	/
AST (U/L)	34.6 ± 13.6	30.2 ± 16.3	0.218	< 40
ALT (U/L)	42.8 ± 20.9	35.9 ± 23.7	0.194	< 40
γGT (U/L)	67.9 ± 60.2	45.1 ± 51.9	0.087	12–64
Fatty Liver Index	69.6 ± 27.3	49.2 ± 31.3	**< 0.001**	0–60
Visceral Adiposity Index	2.6 ± 1.0	2.6 ± 1.1	0.902	1.92–2.52
ALP (U/l)	102.9 ± 47.4	88.1 ± 44.9	0.174	40–150
Na (mmol/l)	141.6 ± 2.6	141.8 ± 4.2	0.897	136–145
K (mmol/l)	4.3 ± 0.5	4.2 ± 0.4	0.628	3.5–5.1
Total calcium (mg/dl)	9.3 ± 0.4	9.4 ± 0.6	0.571	8.4–10.2
Total phosphorus (mg/dl)	3.9 ± 0.8	4.9 ± 0.7	0.318	2.3–4.7
TSH (μIU/ml)	1.1 ± 0.6	1.4 ± 1.1	0.100	0.4–4.3
FT3 (pg/ml)	2.6 ± 0.8	2.9 ± 0.7	**0.041**	2.3–4.3
FT4 (ng/ml)	0.9 ± 0.2	1.1 ± 0.2	**0.042**	0.75–1.7
FSH (mUI/ml)	4.4 ± 4.0[a]	4.4 ± 2.5[b]	0.988	1.4–18.1[a]; 2.5–10.2[b]
		50.3 ± 16.8[c]	**< 0.001**	23–116.3[c]
LH (mUI/ml)	2.2 ± 1.5[a]	5.6 ± 5.2[b]	**0.001**	1.5–9.3[a]; 1.9–12.5[b]
		31.8 ± 8.8[c]	**< 0.001**	15.9-54[c]
17β-estradiol (pg/mL)	40.8 ± 14.3[a]	88.9 ± 29.8[b]	**< 0.001**	< 17.7[a]; 19.5–144.4[b]
		21.1 ± 1.9[c]	**< 0.001**	
Testosterone (ng/ml)	353.2 ± 160.6	/	/	167–778
ACTH 8.00 a.m. (pg/ml)	19.9 ± 18.2	16.9 ± 9.2	0.767	10–130
Cortisol 8.00 a.m. (μg/dl)	10.3 ± 5.2	12.8 ± 5.0	**0.039**	4.3–22.4
UFC (μg/24 h)	84.1 ± 59.5	113.8 ± 69.2	**0.044**	21–292
PRL (ng/ml)	61.9 ± 167.5	16.9 ± 10.6	0.109	5–15
GH (ng/ml)	0.7 ± 1.8	1.4 ± 1.5	0.089	5–10
IGF-1 (ng/ml)	195.8 ± 112.7	245.0 ± 112.7	0.069	76–596

Significant *p* values are been reported in bold

Values are expressed as (mean ± SD). Significant differences between males and females are noted (Student's unpaired *t* test)

BUN blood urea nitrogen, *ALT* alanine transaminase, *AST* aspartate transaminase, *γGT* γ-Glutamyl Tranferase, *UFC* urinary free cortisol, *PRL* prolactin, *IGF-1* insulin-like growth factor-1

[a]vs Males

[b]vs Premenopausal patients (follicular phase)

[c]vs Postmenopausal patients

predominance in non-functioning sellar masses are still conflicting [28, 30, 32].

Although the majority of the available studies indicate a substantially similar prevalence of NFPA in both sexes, there is general agreement that elder male patients harbor macroadenomas more frequently than young patients and females. These patients are also characterized by increased tumor cell proliferation and cancer aggressiveness [2]. In a recent retrospective, multicenter study conducted from 1992 to 2015 and including 189 NFPA, patients with macroadenomas were older than those with microadenomas (59.5 ± 16.7 vs. 46.4 ± 18.1 years, $p = 0.007$) and were

more frequently men (85.7% vs. 58.6%, $p = 0.023$) [33]. Nevertheless, previous studies have reported discordant data. Schaller [32], in a more limited series of 28 patients followed from 1990 to 1997, observed a female-to-male ratio of 1:1.5, but in males tumors were smaller and less invasive at surgery, and their outcome was better than in females. Afterwards, in a Swedish series of 592 patients diagnosed with pituitary adenomas in 2001–2011, NFPA were reported in 54.1% of cases, and 65.4% of them were found in males [34]. Similarly, Agustsson et al. [35], in a retrospective observational study including 471 patients with pituitary adenomas diagnosed in Iceland from 1955 to 2012, reported that NFPA were 43.1% of all adenomas and 51.2% were found in males. Zerehpoosh [36] confirmed that among 278 patients with pituitary adenomas undergoing surgical interventions, 28% presented with NFPA and 66% of them were males. Similarly, Day et al. [37] found 21.5% NFPA, with a similar higher prevalence among males (53%). Vaninetti et al. [38], based on the retrospective analysis of 681 patients within a provincial pituitary registry between January 2006 and June 2014, reported NFPA in 50% of them, but with a slightly higher prevalence in females (64.9 vs. 54.5%). Ntali and Wass [2] grouped 10 research reports and clinical case series on NFPA from 1988 to 2014, and confirmed an higher prevalence of NFPA among males, although variably ranging from 51.2 to 65.4%. More recently, Moreno et al. [39] found in a retrospective clinical study on 44 Spanish patients that all NFPA in this series were macroadenomas, with a very small increased prevalence in females (54.5%), who presented also more frequent adenomas with hormonal and dopamine receptor D_4 expression, but there were no differences between tumor size and need of radiotherapy. Cooper and Melmed [40] reported that there was a male predominance in silent gonadotroph adenomas, the most common type of NFPA, and there were also distinctive gender differences by electron microscopy in the ultrastructure of Golgi apparatus, responsible for glycan processing in glycoprotein synthesis and releasable amount of glycoprotein hormones. By analyzing in detail our series of non-functioning sellar masses, we found no significant gender differences in the prevalence of different histotypes, except for Rathke's cleft cysts that were exclusively found in females. In this context, Katavetin et al. [41] showed an association between the Rathke's cleft cysts and female puberty, suggesting a possible role of sex steroids; other studies showed a sex dependency for the localization of some intracranial arachnoid cysts [42, 43]. However, there were significant gender differences in the size and in the clinical presentation of NFPA. In particular, macroadenomas were significantly more frequent in males than in females, while females showed a higher prevalence of microadenomas. This finding was similar to what occurs for prolactin-secreting adenomas, as reported by Colao et al. [31], although with some degree of discordance [44], likely reflecting a delay in diagnosis linked to a less specific symptomatology in men. In our series, in association with the higher tumor size in males, we found also a slight increase in the compressive symptoms related to mass effect from the pituitary, including headache and visual field defects, although this difference did not reach a statistical significance. Accordingly, hypopituitarism, mainly severe hypopituitarism, was more frequent in males, which presented with higher prevalence of secondary hypothyroidism, hypocortisolism, and hypogonadism than females. Consequently, incidentally discovered lesions NFPA were more commonly in females than in males. No gender differences were however found in doses of the replacement therapies

A further aim of this study was to analyze gender differences in anthropometric measurements and metabolic presentation of patients with NFPA. Considering all variables included, albeit there was no sex difference in obesity prevalence, the prevalence of the metabolic syndrome was more common among males than females. Between the two-cardiometabolic indices included in this study, FLI was also higher in males, while there were no differences in VAI. Nevertheless, it is not possible to exclude influence of age on gender differences in these parameters. Of interest, the prevalence of obesity was two-fold higher among the population of NFPA (28.8%) compared to the adult general population living in Campania region (14.9%) [45]. This finding suggests a role for the higher prevalence of pituitary hormone deficiencies seen in males compared to females as possible endocrine contributor to obesity in patients with NFPA.

Besides the delay in the diagnosis, the higher prevalence of macroadenomas among males let to hypothesize a possible a role of the different sex steroid hormone milieu in affecting the biological behavior of these lesions, although the mechanisms involved are not fully understood.

The disruption of estrogen-induced negative feedback gonadotropin secretion in patients with NFPA has previously reported [46]. Estrogen receptors (ERs) are expressed in both normal pituitary tissue [47] and pituitary adenoma [48, 49] with ERα acting as an oncogene and ERβ as a tumor suppressor [50]. In particular, a positive correlation has been described between ERα expression and tumor growth in invasive macroadenomas [48], and a stronger nuclear ERα expression and weaker ERβ expression have been reported in invasive NFPA compared with non-invasive ones [43]. ERα and ERβ might affect the invasiveness of NFPA through their opposite correlation with the pathway of E-cadherin, an adhesion molecule causally involved in cancerogenesis [51] proposed as markers of NFPA invasiveness at mRNA level [8], and their association in males only with somatostatin

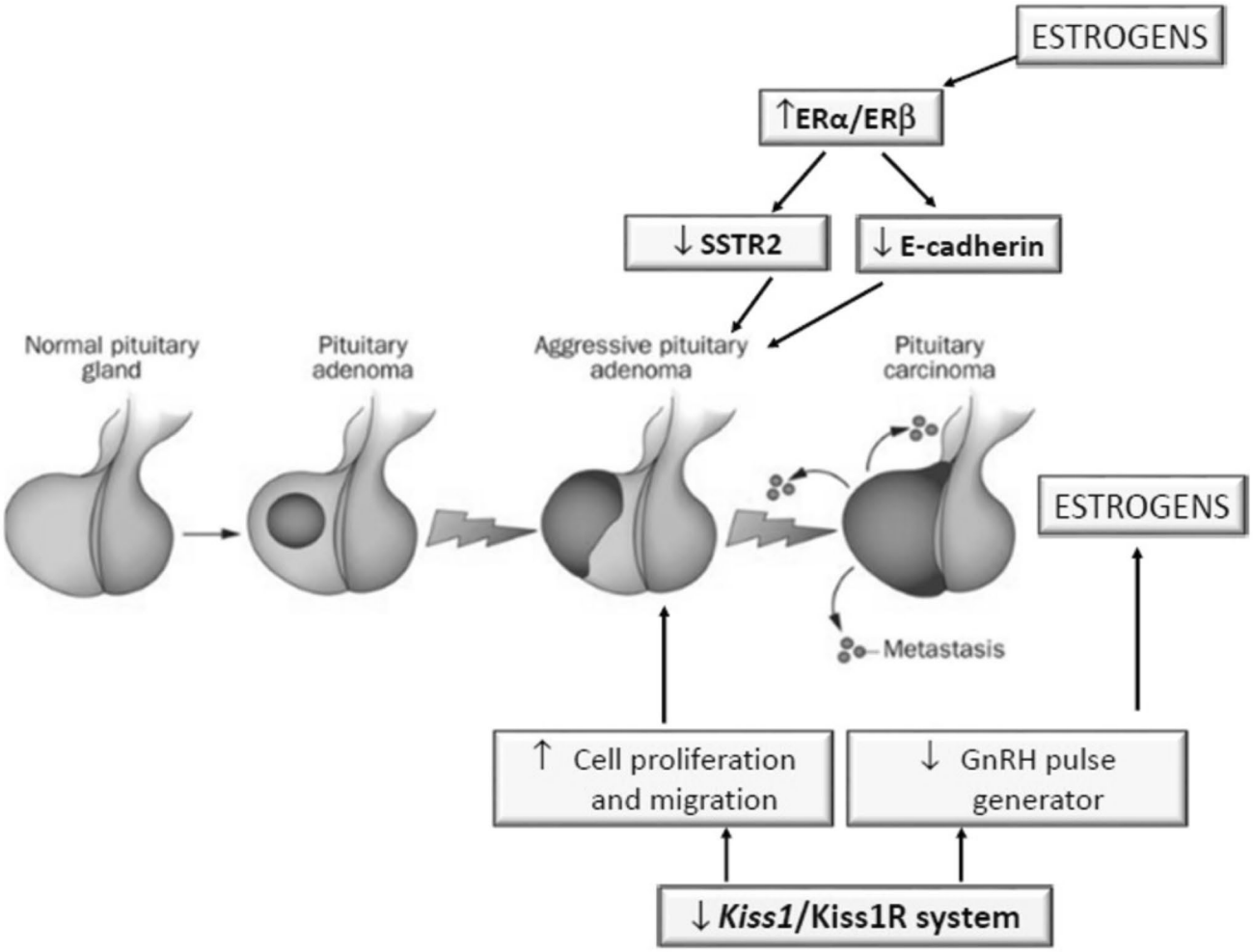

Fig. 2 Hypothetical mechanisms potentially acting between estrogens and clinical behavior of non-functioning sellar masses. SSTR2, somatostatin receptor-2; Kiss1R, Kiss1 Receptor

receptor (SSTR)-2 distribution, a negative regulator of cell proliferation in malignant cells [52].

Experimental evidence on the antimetastatic role of Kiss1 gene in a wide variety of cancers [53] might provide further support on the possible influence of sex steroid hormone on biological behavior of NFPA. As previously reported, most NFPA stems from gonadotropic cells, with immunostaining for gonadrotropins and/or α subunit of glycoprotein hormones [40]. Kiss1 gene, encoding for Kisspeptin, the neuropeptide operating as GnRH pulse generator in the complex integrated neuroregulation of the metabolic control of reproduction linked to energy status and circadian rhythms [54], is expressed also in pituitary cells. A role for the Kiss1/Kiss1 receptor (R) system in the control of not only gonadotropins but also of other pituitary hormones has been previously reported [55]. Martınez-Fuentes et al. [56] firstly reported that Kiss1/Kiss1R system, which can exert functional, proapoptotic actions, was defective in 40% of NFPA, while Yaron et al. [57] found that Kiss1R was expressed in the majority of human NFPA, with a clear female predominance (81% vs. 50% males), albeit without a defined association with tumor size or invasiveness. In Fig. 2 is represented the hypothetical mechanisms potentially acting between sex steroids and clinical behavior of NFPA.

There are several limitations that need to be addressed in this study. Firstly, the observational design of the study does not allow estimation of the cause and effect relationship between gender and clinical behavior of non-functioning sellar masses. Secondly, our findings are based on evidence from a single-center study population. Nevertheless, the sample of non-functioning sellar masses included in this study was largely representative of the real distribution of these lesions compared with that obtained by other multicentric studies, and it was sufficiently homogeneous relatively to potential confounding variables, such as the geographical provenience or different environmental factors. Thirdly, information on subsequent clinical course of the non-functioning sellar masses to better define the effect of gender on cancer behavior are lacking. Finally, we did not evaluated

the expression of histological and molecular markers of proliferation/invasion to better define the gender differences in NFPA characteristics in our sample population.

In conclusion, the results of this study, the first to explore the presence of gender differences in NFPA in an Italian series of newly diagnosed non-functioning sellar masses, showed that, according to the literature, the size of NFPA and, consequently, also the occurrence of multiple pituitary hormone deficiency were significantly higher in males than in females, while a lower prevalence of incidentally discovered NFPA in males. Obesity was frequently found among NFPA, without a significant gender difference, but some metabolic consequences were more common among males than females. Therefore, apart from the possible delay in the diagnosis induced by the gender differences in symptom presentation, the higher prevalence of macroadenomas amongst NFPA in males compared with females let to hypothesize a key role of the sex hormone profile as predictive factors of their biological behavior and metabolic consequences. Further studies in larger series, with the inclusion of histological and molecular markers of proliferation/invasion and, possibly, in multicentric studies, are however mandatory to better support the influence of gender differences on onset and progression of NFPA.

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Informed consent All patients signed their informed consent. Consent for publication: The study design was made in accordance with the Helsinki II Declaration for Study on human experimentation and approved by the local ethic committee (n. 63/97),

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