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Clinically non-functioning pituitary incidentalomas: characteristics and natural history

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ABSTRACT

Introduction: available data on pituitary incidentalomas mostly derive from small-scale studies, with heterogeneous inclusion criteria and limited follow-up. No paper has focused specifically on clinically non-functioning pituitary incidentalomas (CNFPIs).

Objective: to describe the characteristics and the natural history of patients diagnosed with CNFPIs.

Methods: retrospective multi-center cohort study evaluating hormonal, imaging and visual field characteristics at diagnosis and during follow-up of CNFPIs investigated in two Pituitary Centers.

Results: 371 patients were included (50.9% microadenomas, 35.6% males). Men were older and more likely to have a macroadenoma ($p < 0.01$). 23.7% of patients presented secondary hormonal deficits (SHDs), related to tumor size (higher in macroadenomas; $p < 0.001$) and age (higher in older patients; $p < 0.001$). Hypogonadism was the most frequent SHD (15.6%).

296 patients had follow-up data; 29.1% required surgery after first evaluation, 97 had at least 3 years of follow-up. 15.3% adenomas grew (more macroadenomas), but only in microadenomas patients with longer follow-up showed a higher growth-trend. 5.2% of patients developed new SHDs (micro- vs. macroadenomas $p = 1.000$), and in 60% of them this was not associated with an increase in tumour size. Thirteen additional patients required surgery during follow-up (1 microadenoma at diagnosis).

Conclusions: Macroadenomas and age are risk factor for SHD in CNFPIs, which occur at diagnosis in a quarter of patients. During follow-up, macroadenomas tend to grow more often, but microadenomas display higher growth-trend as follow-up increases. Deterioration of pituitary function is not always related to adenoma growth.

INTRODUCTION

The widespread use of neuroradiological imaging has resulted in the increasing discovery of collateral findings within the pituitary gland, unrelated to the indication for the original scan. These lesions are called “pituitary incidentalomas” (PIs) (1) and their prevalence is now reported to be around 10% of general population (based on different evaluation modalities) (2, 3). Clinically non-functioning pituitary adenomas are the most frequent putative lesions, representing about three quarters of PIs (1, 2).

PIs are a challenge due to the lack of conclusive data regarding their clinical relevance, natural history and proper management; in particular, the only available meta-analysis (4) reports significant heterogeneity of data due to different inclusion criteria used in different papers (functioning vs. non-functioning PIs, inclusion of both patients with incidentally and clinically discovered pituitary adenomas), short follow-up and small size of the cohorts, with only 3 series including more than 100 patients (2, 5, 6).

Therefore, current available data are not strong enough to draw any evidence-based conclusions. No study has specifically focused clinically non-functioning pituitary incidentalomas (CNFPIs). Moreover, although secondary hormonal deficiencies (SHD) are frequently described in these patients (13–46% of cases) (5-7) little is known regarding their risk factors at diagnosis and during follow-up.

The aim of this study was to analyze the characteristics and the natural history of a large cohort of patients with clinically non-functioning pituitary incidentalomas (CNFPIs), either followed up conservatively or surgically treated.

MATERIALS AND METHODS

Study design and setting

In this observational multicenter retrospective study, we analyzed data of a cohort of patients diagnosed with CNFPIs and evaluated at two Endocrine Units between 1980 and 2018: "Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico" in Milan, and "IRCCS Humanitas Research Center" in Rozzano, Milan.

Inclusion criteria were (i) detection of a pituitary lesion on a brain imaging (CT, MRI or other) performed for reason not linked to a confirmed pituitary dysfunction or compressive symptoms (ii) pituitary mass with imaging characteristics (as judged by an experienced neurosurgeon and/or directly obtained from the radiology report) and/or histology (for patients in which this was available) suggestive for pituitary adenoma. Patients who presented with headache were included only if, by clinical judgment, the lesion was not the cause of headache and/or if another cause of headache was present. We also included in our cohort patients in which a pituitary MRI was erroneously prescribed by another specialist for a suspected alteration of pituitary function later not confirmed (e.g. stress-related hyperprolactinemia with subsequent confirmed normal resting values, clinical feature but no biochemical evidence of pituitary disease, etc.). Since these alterations were eventually not confirmed, these patients did not have an indication for pituitary MRI, and therefore the pituitary finding was deemed to be incidental.

Exclusion criteria were (i) evidence of pituitary hormone hypersecretion (ii) missing data regarding hormonal evaluation at diagnosis.

Evaluation at diagnosis

Initial biochemical evaluation included: 1) for pituitary-adrenal axis morning serum ACTH and cortisol levels and cortisol response after ACTH 1 µg or ITT (with cutoff value of 500 nmol/l at 30' or 60' (8)); 2) for pituitary-GH axis, IGF-1 levels (compared with normal values range specific for age and sex), and GH response to GHRH + arginine (with cutoff value of 11.5 / 8 / 4.2 ng/ml for lean/overweight/obese patients (9)) or ITT (with cutoff value of 3 ng/ml). We

performed this test systematically only in the most recent years; 3) for pituitary-thyroid axis, serum TSH and FT4 levels; 4) serum PRL level after 60' resting period; 5) for pituitary-gonad axis, in females serum LH, FSH and estradiol levels (except in patients with regular menstrual cycles) and in males serum LH, FSH and testosterone levels. In case of borderline low levels of testosterone (8-12 nmol/l), we checked SHBG and albumin to calculate free testosterone levels (10). Diagnosis of GHD was also made without biochemical testing in the presence of three other documented SHD and features of GHD, in accordance with current guidelines (11).

At diagnosis, all patients also underwent hypothalamus-pituitary focused MRI (with contrast when it entered clinical practice). Visual field (VF) evaluation was performed as per guidelines (macroadenomas or lesions that abutted or compressed the optic pathway) (12).

Follow-up

During follow-up, patients were evaluated after 6-12 months from diagnosis and then less frequently, based on clinical judgement. This included:

- unstimulated hormonal tests, as specified above (dynamic tests were repeated only if a new pituitary deficit was suspected based on clinical judgement);
- hypothalamus-pituitary focused MRI.;
- VF evaluation (based on clinical judgement or radiological evidence of optic pathway involvement).

Data at diagnosis and at the last follow-up were compared for patients who did not undergo surgery. Adenomas were defined as stable, increased or reduced in dimension according to radiological report and/or review of MRI by an experienced endocrinologist or neurosurgeon.

Statistical analysis

Continuous variables were described as mean and standard deviation or median and interquartile interval, while categorical variables were described as number and percentage. For continuous variables, differences between groups were analysed using student t test or

Mann Whitney test as appropriate; for categorical variables, differences between groups were analysed using Chi square test or Fisher's exact test as appropriate. P values < 0.05 were considered statistically significant. The statistical analysis was performed using Stata 15.

RESULTS

Baseline characteristics

371 patients were included, of whom 132 were males (35.6%). The baseline characteristics of our population are shown in Table 1. Mean age at diagnosis was 50 ± 18 years, with women being younger than men by about a decade (46 ± 17 vs 57 ± 17 years, $p < 0.01$). The most frequent indications for brain imaging were ear, nose and throat (ENT)/ neuroophthalmological disturbances not related to mass effect (216 patients, 58.2%). However, the symptoms that prompted investigations showed a different distribution between genders, with females being more frequently investigated for suspected alteration of pituitary function later not confirmed [64/239 (26.8%) vs. 14/132 (10.6%), $p < 0.001$] and headache [36/239 (15.1%) vs 8/132 (6.1%), $p = 0.011$].

In our population, micro and macroadenomas were almost equally represented (51.9 and 49.1% respectively); however, subdividing the population based on gender, we found that males were more likely to have a macroadenoma [104/132 (78.8%) vs 78/239 (32.6%), $p < 0.001$]. Patients evaluated for suspected alteration of pituitary function later not confirmed were more likely to have a microadenoma, probably due to the dedicated pituitary MRI they underwent as first imaging modality.

At the first hormonal evaluation, performed in most cases within one year after diagnosis, 23.7% patients (88/371) had SHD. Male sex, age at diagnosis and having a macroadenomas were found to be predictive of SHD when analyzed by univariate analysis. Specifically, being diagnosed after 65 years old doubled the risk of having a pituitary deficit (OR 2.49, 95% CI 1.48-4.19, $p = 0.001$). In multivariable analysis, only age at diagnosis and having a macroadenoma maintained statistical significance (Table 2). The most frequently diagnosed SHD was hypogonadism (15.6%), followed by hypoadrenalism (10.2%), GHD (8.4%) and hypothyroidism (5.1%); 15.1% of patients had hyperprolactinemia. Looking at specific SHD separately, all deficits were more frequent in male and macroadenomas, apart from hypoadrenalism, which however showed a tendency towards statistical significance

when comparing incidence in micro vs. macroadenomas (p = 0.086), while no difference was observed regarding gender. These associations were maintained in multivariable analysis only for hypogonadism and GHD.

11.1% (21/189) of patients with microadenomas had SHD at diagnosis. The exact diameter at diagnosis was available for 135 of these patients, and we could not find any statistically significant difference in SHD prevalence between patients with microadenomas above or below 5 mm [9/52 (17.3%) vs 8/83 (9.6%) respectively, p = 0.286] and in the prevalence of any specific deficits (Table 3). To evaluate the potential impact of different biochemical assays used throughout the long period of evaluation, we stratified patients according to decade of pituitary function evaluation; the prevalence of any SHD and of specific SHD did not show a significant change through time (Figure 1).

Visual field (VF) at diagnosis was available for 177 patients (145 macroadenomas and 32 microadenomas) and showed a VF deficit in 63 patients (35.6%). Macroadenomas caused more frequently a VF alteration compared to microadenomas [58 (40.0%) vs 5 (15.6%) respectively, p = 0.008].

Follow-up

Data on follow-up were available for 296 patients (79.2% of the whole cohort): 86 underwent surgery after the first evaluation, while 210 were managed conservatively. Of these 97 (46.2%) had at least 3 years of both radiological and hormonal follow-up (Table 4).

Radiological follow-up data were available for 203 patients, with a median time from diagnosis of 3 years (IQR 2-5 years). 117 patients (57.6%) had a radiological follow-up of at least 3 years. 31 PIs (15.3%) showed an increase in size and 31 (15.3%) a decrease; macroadenomas were more likely to grow over time [19/71 (26.8%) vs 12/132 (9.1%), p = 0.001], while microadenomas were more likely to reduce in size [28/132 (21.2%) vs 4/71 (5.6%), p = 0.004] (Figure 2). In the univariate analysis, an association between male gender and adenoma growth was also observed, but this was not confirmed in multivariate analysis (Table 5). When looking at growth-trend subdividing the cohort in micro and

macroadenomas based on the length of available follow-up, the figures for macroadenomas did not show a significant change over time (figure 3A). However, the percentage of grown microadenomas increased steadily for the first eight years (figure 3B), and when comparing growth rate in patients with at least 6 years of follow-up to patients with shorter follow-up the first group showed a higher percentage of grown adenomas, albeit non-strictly significant (6/32 vs. 6/100; p = 0.07).

Hormonal follow-up was available for 194 patients, with a median time from diagnosis of 3 years (IQR 2-5 years). 111 patients (57.2%) had a hormonal follow-up of at least 3 years. 5.2% (10 patients) developed a new SHD, with male patients having a higher risk of new onset SHD compared to women [6/46 (13.0%) vs. 4/148 (2.7%), p = 0.013]; no association was observed with the initial diameter of the lesion [3/62 (4.8%) vs 7/132 (5.3%) in macro and microadenomas respectively, p = 1.000] and age at diagnosis (51±16 years in patients with a deterioration in pituitary function vs 46±18 years in patients with a stable function, p = 0.352). Of these 10 patients, 7 had normal pituitary function at baseline and 3 already had partial hypopituitarism; we detect 6 cases of new onset hypoadrenalism, 3 cases of growth hormone deficiency, 2 cases of hypothyroidism and 1 case of hypogonadism.

Data on both imaging and hormonal follow-up were available for 187 patients, and were concordant in 181 patients; however, 6 patients showed a deterioration of pituitary function even in the presence of a stable or reduced adenoma.

VF follow-up was available for 39 patients, with a median time from diagnosis of 3 years. VF was stable in most patients (28 patients, 71.8%), worsened in 9 patients (23.1%) and improved in 2 (5.1%). We did not show an association of deterioration of visual field and diameter at diagnosis, probably due to the small number of patients with VF follow-up [8/30 (26.7%) in macroadenomas vs 1/9 (11.1%) in microadenomas, p = 0.654].

Ninety-nine patients underwent surgery (33.4% of the 296 patients for whom follow-up information was available; macroadenomas 98%). In 86 cases surgical indication was formulated at diagnosis, while 13 patients met the surgical criteria during follow-up (median

time of 4 years). This was due to growth of the lesion and/or deterioration of visual field; of these patients, one had a microadenoma at diagnosis, which was operated after 7 years of follow-up.

DISCUSSION

In this retrospective multicentric study we evaluated one of the largest cohort of patients with PIs described in literature, focusing on CNFPIs evaluated during nearly four decades in two Italian Pituitary referral centers. Papers on pituitary incidentalomas are mostly small-scale studies (4) or have a heterogenic definition of pituitary incidentalomas (2, 5), leading to the inclusion of lesions with a different natural history and therapeutic approaches. In this paper, our stricter inclusion criteria, our large cohort with a long follow-up allowed us to better define some of the characteristics of the most common type of PIs.

CNPIs in our cohort were more commonly diagnosed during the fifth decade and in female patients, similarly to other studies (4, 6, 7). While micro and macroadenomas were almost equally represented, we found a significant difference in tumour size between genders, with men more likely to have a macroadenoma. This is probably related to the greater time to diagnosis of PIs in these patients, due to the underestimation of headache and sexual dysfunction in men. Indeed, the different distribution of indications for imaging between genders in our cohort (males being less frequently investigated for suspected alteration of pituitary function and headache compared to women) seems to confirm this observation.

In our cohort the most common indication for imaging was neuroophthalmological/ENT problems; this is different from what described by other groups, which found headache as the most common indication for brain imaging leading to the diagnosis of PIs (2, 6, 7). The association of headache and pituitary masses is controversial (13), and we therefore decided to include only those patients in whom headache was judged not to be associated with the presence of the adenoma. This probably accounts for the lower figures for headache as an indication for imaging in our cohort compared to the one reported in other studies (11.9% vs. around 30% in published papers) (2, 7). While this might have led us to exclude some patients in which headache was not caused by the sellar mass, this have allowed us to be more confident that we have included only patients with an incidental imaging finding, i.e. true PIs. This probably also explain the lower incidence of

macroadenomas in our paper compared to others clinical series of pituitary incidentalomas (2, 5, 6).

A significant proportion of our patients had secondary hormonal deficiency (SHD) at diagnosis: 36.8% of macroadenomas and 11.1% of microadenomas. While the different SHD incidence between micro and macroadenomas is well known in literature (5, 7), we are the first to describe an association between age at diagnosis and pituitary deficits. When analysing specific deficit, we confirmed this observation for both hypogonadism and GHD, but not for the other deficits. While the association of hypogonadism with age might also be explained by late onset hypogonadism unrelated to the adenoma (14), showing this trend for multiple SHDs reduce the likelihood of this to be a random finding. This could be explained by a longer time to diagnosis or by a reduced capacity of the pituitary in the elderly to cope with an expanding mass and highlights the importance of a full hormonal evaluation especially in patients above 65 years old, in which the risk of SHDs appears to be more than doubled compared to younger patients. Looking at the influence of diameter at diagnosis on SHD, we could not find any difference between small micro CNFPIs (≤ 5 mm) and larger micro CNPIs (> 5 mm). This could be due to the small sample size of these groups; however, in the absence of clear evidence that small micro CNFPIs have lower or no risk of SHD, every patient with CNFPIs should be screened for hypopituitarism regardless of the size.

About half of our cohort had a follow-up of more than 3 years; most adenomas remained unchanged in size (69.5%) and showed a stable pituitary function (94.8%). Macroadenomas showed a higher propensity to growth in time compared to microadenomas through time (26.8 vs. 8.3%). However, when looking at the growth-trend in time subdividing the cohort in micro and macroPIs, the percentage of macroadenomas that grew was stable through time. On the other hand, the percentage of grown microadenomas increased steadily as follow-up increased, reaching a plateau after 8 years (probably due to the small number of patients with such a long follow-up). Comparing patients with microPIs with at least 6 years of follow-

up to patients with shorter follow-up, we found a higher growth rate in the first group, with borderline significance (p = 0.07). This difference in behavior between micro and macroPIs might be explained by the fact that macroadenomas with a higher propensity of growth already met surgical indication at diagnosis, and by operating on these patients, we selected for follow-up macroPIs with a lower risk of growth, possibly not representative of all macroadenomas. Microadenomas, on the other hand, are rarely operated on at diagnosis, and this allowed us to have a cleaner and more reliable follow-up for these patients. While this growth has rarely led to surgery in our cohort (only one in 12 microPIs met surgical criteria during follow-up), we have a relatively short follow-up compared to the one that these patients will probably experience during their lifetime. Considering the increase in life expectancy and since these masses are diagnosed in the 4^{th}-5^{th} decade of life, we could expect to follow-up these patients for 20 to 30 years in the future. Given the trend we saw in our population, it is possible that the number of patients that will meet surgical criteria during follow-up will increase. Therefore, it is important not to discharge these patients, but to continue to follow them up lifelong.

Our rate of tumor reduction during follow-up was similar to the one reported for nonfunctioning adenomas and pituitary incidentalomas in other studies, ranging from 10 to 20% (15, 16). This might be attributed to ischemic changes within the tumor, as speculated by other authors (16).

Finally, only a minority of patients developed new hormonal deficits, and we could not find any association between incident SHD and diameter at diagnosis; however, this might be related to the small number of patients with this event. Interestingly, only 40% of these patients had a visible growth of the adenoma at the MRI, while in the remaining the MRI was stable or showed a reduction of the adenoma during follow-up. This finding might be explained by a small change in the dimension of the adenoma not visible at MRI, or by a small paucisymptomatic bleeding within the adenoma, capable anyway of causing changes in the pituitary function. While some guidelines do not suggest routine follow-up endocrine

testing for microadenomas whose clinical picture does not change (12, 17), this finding underline the need to routinely testing all patients during follow-up, even in the absence of imaging changes.

Our study has several strengths. We analyzed data from two Pituitary referral centers during a long period of time, and this allowed us to include a large number of patients in this study. This is one of the few series available in literature to include more the 300 patients with pituitary incidentalomas (506 patients in the Sanno et al. and 328 in the Imran et al. papers) (2, 5), and the largest one from Europe. Another strength of our study was the decision to include only patients with characteristics compatible with clinically non-functioning pituitary incidentalomas, reducing heterogeneity in our cohort. This is in fact the largest cohort of CNFPIs available in literature. There are some limitations as well: firstly, due to the retrospective nature of this paper, some information on diagnosis and on follow-up data were missing (in total, 20.8% of patients were lost at follow-up); this might have had some influence on our results, since patients with symptomatic growth are more likely to come back to clinic compared to not-symptomatic patients. Secondly, we analyzed data of patients evaluated in two referral Pituitary Centers and therefore subject to referral bias; our data may therefore not be necessarily representative of all CNFPIs. Thirdly, since dynamic testing for GHD was only performed systematically in the past years, the actual incidence of this deficit is probably underestimated in patients diagnosed before 2000; moreover, different laboratory kit with different analytical sensibilities have been used over time, which might have possibly accounted for a difference in the incidence of deficits. However, when looking at the prevalence of SHDs in different decades of diagnosis (figure 1) we could not find any difference of their prevalence through time, indicating that this effect was probably reduced. Finally, our paper does not include a control group, and this might have influenced our follow-up findings especially in macroPIs, since by operating on these masses we have probably selected patients with a different natural history; however, this is a limitation difficult to deal with, since it would be unethical not to operate on patients with surgical indication.

In conclusion, in this paper we described the largest series of clinically non-functioning pituitary incidentalomas to date. CNFPIs are more frequently diagnosed in female patients, but male patients are more frequently found to have a macroadenoma. Secondary hormonal deficiencies are present in about a quarter of patients at diagnosis, with patients with macroadenomas and older patients being at higher risk for hypopituitarism; however up to 11.1% of microadenomas have SHD. About a third of patients required immediate surgery after diagnosis, mostly due to asymptomatic visual field deficit. Only a minority of PIs followed up conservatively tended to grow or to cause additional hormonal deficiency; however, since these two events are not always related, it is important to perform both radiological and biochemical periodical follow-up. In our cohort microadenomas with longer follow-up, especially beyond 6 years, seemed to display a higher propensity for growth compared to microPIs with a shorter follow-up; therefore, we suggest continuing following up these patients thought time, although with reduced frequency, since some of them might eventually meet surgical criteria. Further studies are needed to evaluate this aspect, especially in consideration of the increase in life expectancy which will expose these patients to longer follow-up.

STATEMENT OF ETHICS

Subjects gave their written informed consent for the use of their clinical data for research purposes. Ethics Review Committee approved the study protocol.

DISCLOSURE STATEMENT

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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AUTHOR CONTRIBUTIONS

A.S. Tresoldi designed the study, collected and interpreted the data and wrote the manuscript. G. Carosi, E. Sala, N. Betella and G. Del Sindaco collected and interpreted the data. E. Morenghi analyzed the data and provided intellectual input. G. Mantovani, A.G.A. Lania, G. Mazziotti, A, Spada, M. Arosio, C. Giavoli, and E. Ferrante devised the project and critically reviewed the manuscript. All authors approved the final version of the manuscript.

FIGURE LEGEND

Figure 1 – Different incidence of SHD and of different pituitary deficits through different decades (below the bars: number of patients evaluated during each time period)

Figure 2 – Radiological follow-up of micro and macroadenomas

Figure 3 - Incidentalomas growth through time. A: macroadenomas. B: microadenomas. (bars: percentage; below the bars: total number of patients with a given follow-up)

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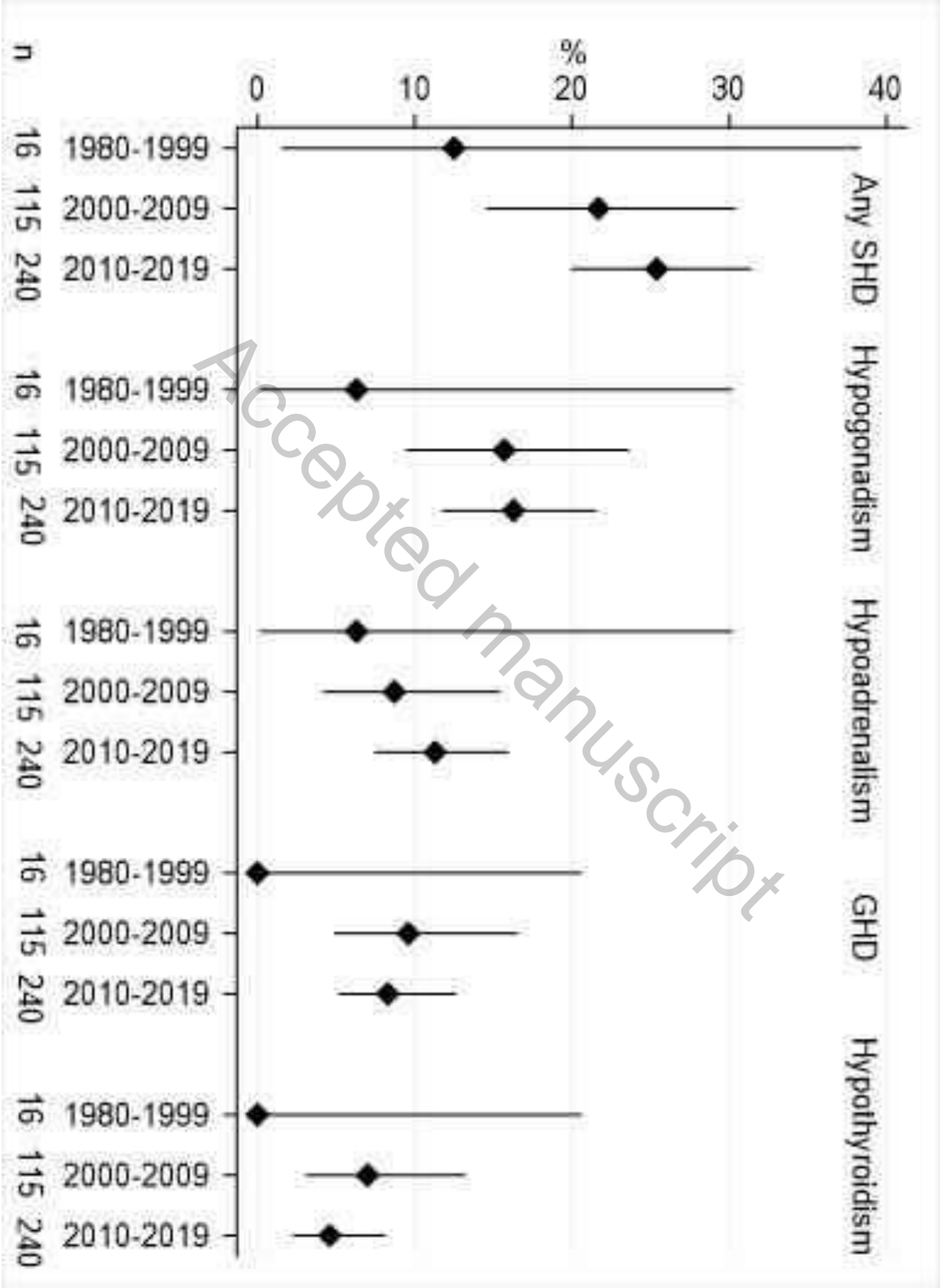

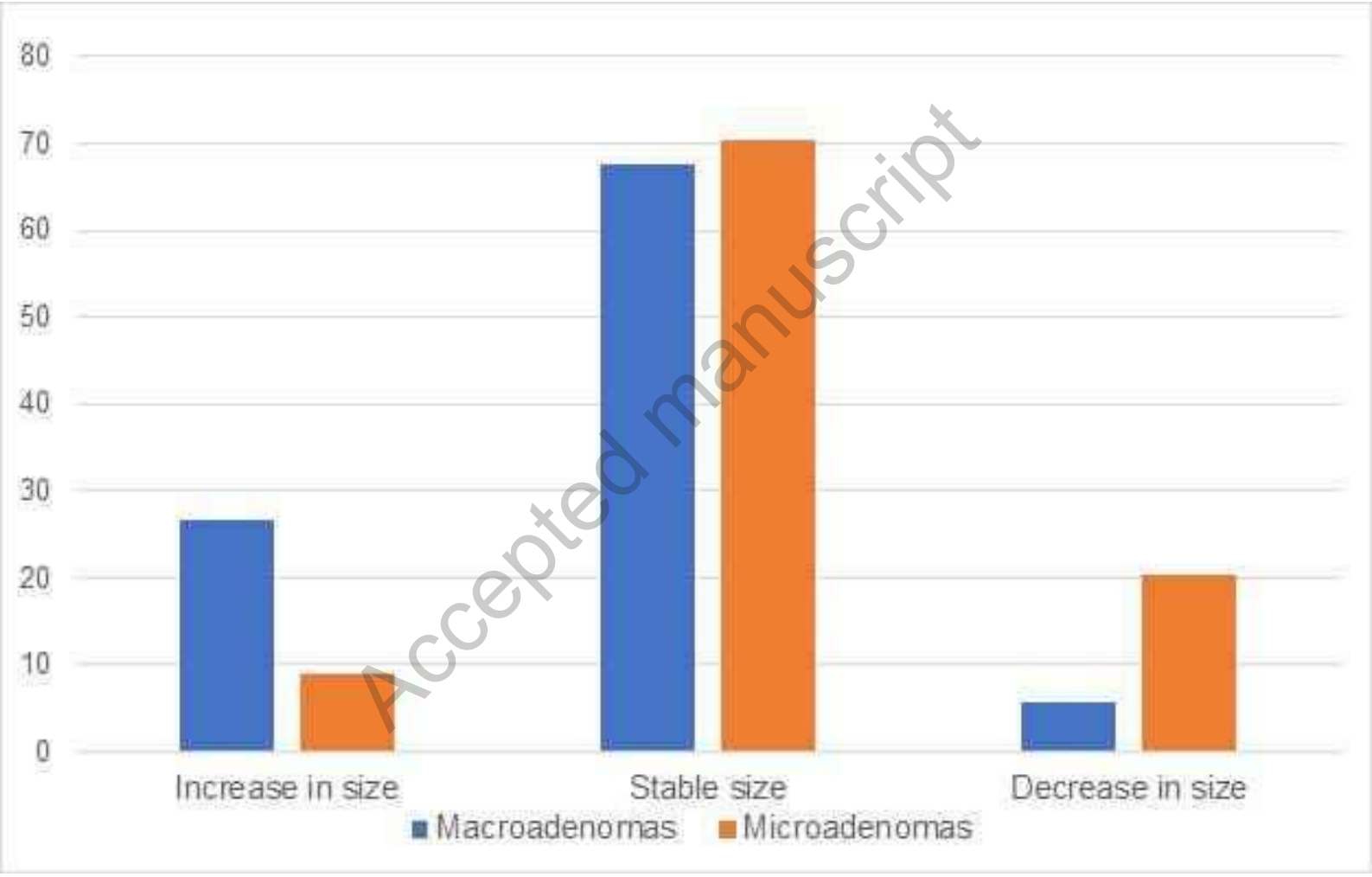

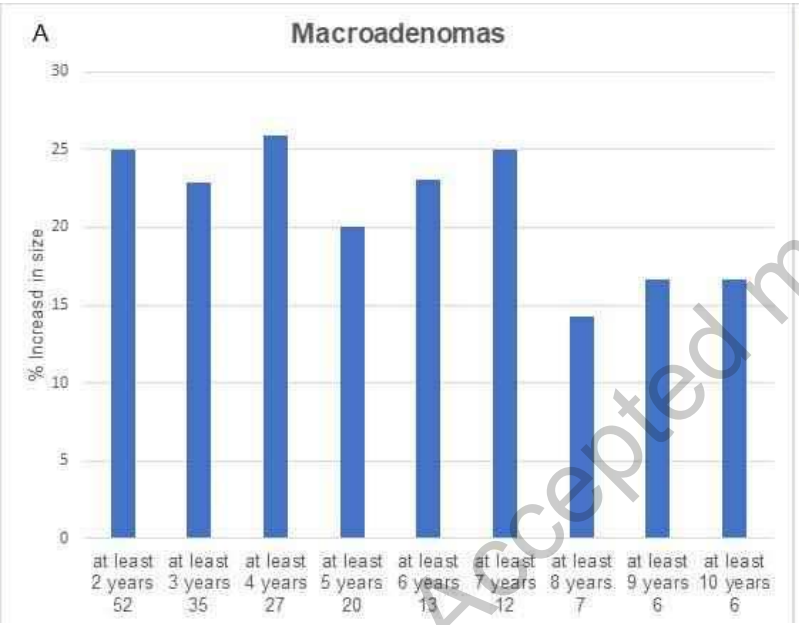

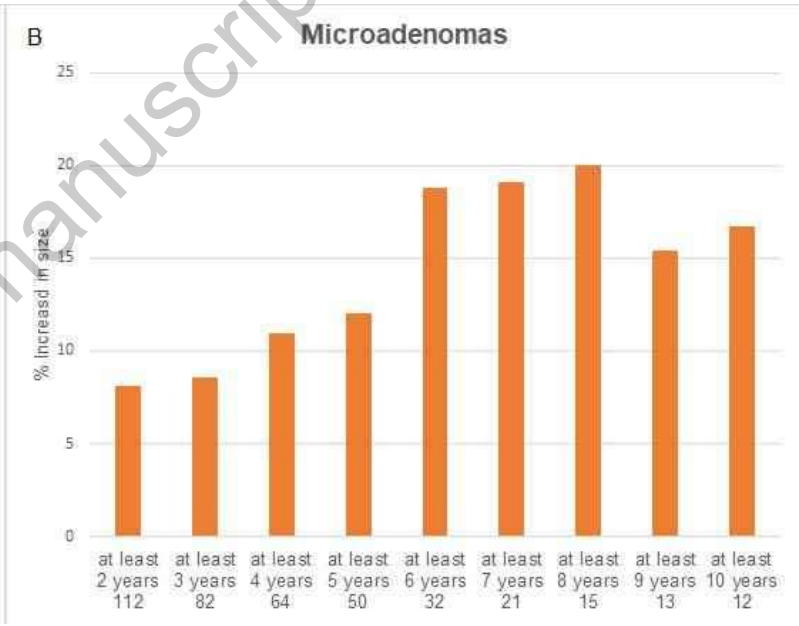

Table 1 – Characteristics at baseline of our cohort

Males, n (%)	132 (35.6%)
Mean age at diagnosis, years ± SD	50 ± 18
Indications for brain imaging, n. (%)	
Neuroftalmological/ENT symptoms	216 (58.2%)
Suspected pituitary dysfunction (later not confirmed)	78 (21.0%)
Headache	44 (11.9%)
Other reasons	33 (8.9%)
Size at diagnosis	
Macroadenomas, n. (%)	182 (49.1%)
Median size (n = 265) (IQR)	9 (5-16)
First hormonal evaluation	
Years from diagnosis, median (IQR)	0 (0-1)
1 deficit, n. (%)	57 (15.4%)
2 deficits, n. (%)	14 (3.8%)
3 deficits, n. (%)	7 (1.9%)
4 deficits (i.e. panhypopituitarism), n. (%)	10 (2.7%)
Type of deficit, n. (%)	
Hypogonadism	58 (15.6%)
Hypoadrenalism	38 (10.2%)
Growth hormone deficiency	31 (8.4%)
Hypothyroidism	19 (5.1%)
Hyperprolactinemia	56 (15.1%)
Visual field deficit (n = 177)	63 (35.6%)

ENT = ear, nose and throat

Table 2 – Variables associated with the presence of secondary hormonal deficits at diagnosis

	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Gender (M vs. F)	2.84 (1.74 - 4.65)	< 0.001	-	-
Tumor size (macro- vs. microadenoma)	4.66 (2.70 - 8.03)	< 0.001	3.38 (1.81 - 6.29)	< 0.001
Age	1.04 (1.02 - 1.05)	< 0.001	1.02 (1.00 - 1.03)	0.041

Table 3 – Incidence of different hormonal alteration at diagnosis

	Male	Female	p	Microadenoma	Macroadenoma	p	Micro ≤ 5 mm	Micro > 5 mm	p
n	132	239		189	182		83	52	
At least on deficit	48 (36.4)	40 (16.7)	< 0.001	21 (11.1)	67 (36.8)	< 0.001	8 (9.6)	9 (17.3)	0.286
Hypogonadism	41 (31.1)	17 (7.1)	< 0.001	3 (1.6)	55 (30.2)	< 0.001	2 (2.4)	1 (1.9)	1.000
Hypoadrenalism	17 (12.9)	21 (8.8)	0.216	14 (7.4)	24 (13.2)	0.086	5 (6.0)	6 (11.5)	0.335
Growth hormone deficiency	22 (16.7)	9 (3.8)	< 0.001	3 (1.6)	28 (15.4)	< 0.001	1 (1.2)	2 (3.9)	0.559
Hypothyroidism	14 (10.6)	5 (2.1)	0.001	2 (1.1)	17 (9.3)	< 0.001	0	1 (1.9)	0.385
Hyperprolactinemia	28 (21.2)	28 (11.7)	0.014	10 (5.3)	46 (25.3)	< 0.001	4 (4.8)	4 (7.7)	0.484

Data are expressed as number (percentage)

Table 4 - Follow up

Total number of patients	296 (79.8%)
Radiological follow up (n = 203)	
Median length, years (IQR)	3 (2-5)
Follow up ≥ 3 years (n.)	117
Follow up ≥ 5 years (n.)	70
Follow up ≥ 10 years (n.)	18
Trend	
Stable dimension	141 (69.5%)
Increase in size	31 (15.3%)
Reduction of size	31 (15.3%)
Hormonal follow up (n = 194)	
Median length, years (IQR)	3 (2-5)
Follow up ≥ 3 years (n.)	111
Follow up ≥ 5 years (n.)	53
Follow up ≥ 10 years (n.)	10
Trend	
Stable function	184 (94.9%)
New SHD	10 (5.2%)
Type of new onset deficit	
Hypogonadism	1/181 (0.6%)
Hypoadrenalism	6/177 (3.4%)
GHD	3/185 (1.6%)
Hypothyroidism	2/189 (1.1%)
Visual field follow up (n = 39)	
Median length, years (IQR)	3 (2-4)
Trend	
Worsened	9 (23.1%)
Stable	28 (71.8%)
Improved	2 (5.1%)

SHD = secondary hormonal deficiency

Table 5 – Variables associated with the radiological growth of clinically non-functioning pituitary incidentalomas

	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Gender (M)	2.55 (1.15 – 5.66)	0.022	1.77 (0.75 – 4.15)	0.191
Macroadenoma	3.65 (1.65 – 807)	0.001	3.11 (1.35 – 7.14)	0.008
Age	1.01 (0.99 - 1.04)	0.180	-	-