TABLES

Table 1: Evidence Table

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Cazabat L, Bouligand J, Salenave S, Bernier M, Gaillard S, Parker F, Young J, Guiochon-Mantel A, Chanson P (2012)[37]	Prospective, single-center study. The entire coding sequence of the AIP gene was screened for germline mutations in 113 patients with non-functioning pituitary adenomas. A subgroup of patients was screened for large deletions or duplications of the AIP and MEN1 genes by multiplex ligation-dependent probe amplification.	Diagnostic / II	AIP mutations were detected in one of 113 patients with nonfunctioning adenomas (0.9%). This large prospective cohort study confirms the very low prevalence of germline AIP mutations in patients with apparently sporadic pituitary adenomas.
Pawlikowski M, Kuta J, Fuss-Chmielewska J, Winczyk K (2012)[33]	A retrospective observational study at a single institution. Fifty-six patients with pituitary adenomas who underwent TSS were included in the study. Thirty-seven patients before the surgery with clinically nonfunctioning pituitary adenomas (CNFPAs) were diagnosed.	Diagnostic / III	Among the pituitary tumors diagnosed before the surgery as clinically nonfunctioning, 45.9% showed GH immunopositivity. The authors concluded that GH immunopositivity occurs in nearly half of “clinically” nonfunctioning pituitary adenomas, and they recommend that IGF-1 determination in blood before the surgery and immunohistochemical examination of adenoma for GH after the surgery should be performed as standard in all patients suffering from pituitary tumors irrespective of the presence or absence of acromegaly symptoms.

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Hong JW, Lee MK, Kim SH, Lee EJ, et al (2010)[20]	Retrospective study to evaluate characteristics that discriminate prolactinoma from non-functioning pituitary macroadenoma with hyperprolactinemia. We included 117 patients with hyperprolactinemic pituitary macroadenomas. Patients were divided into 3 groups: prolactinoma that responded to dopamine agonist (DA) treatment (PRDA); prolactinoma requiring surgical treatment (PRS); and non-functioning pituitary adenoma with hyperprolactinemia (NFPAH).	Diagnostic / II	Old-age low serum prolactin levels and extrasellar extension were associated with NFPAH. Most patients with NFPAH had serum prolactin levels less than 100 ng/ml. GH deficiency was more common in patients with NFPAH compared with patients with PRS and PRDA, without difference of tumor size. Galactorrhea and amenorrhea were less frequent in patients with NFPAH than in patients with PRS and PRDA. In conclusion, old age, extrasellar tumor extension with relatively low prolactin levels, visual defect, and GH deficiency were considered suggestive of non-functioning pituitary adenoma.
Cury ML, Fernandes JC, Machado HR, Elias LL, Moreira AC, Castro M (2009)[12]	Retrospective study of a Southeast Brazilian experience of NFPA in which 104 patients were evaluated by the same team of endocrinologists and neurosurgeon. Patients underwent biochemical evaluation radiological studies and visual field assessment.	Diagnostic / II	Hypopituitarism and neuro-ophthalmological defects were observed in 89%. The authors also observed GH deficiency (81.4%), hypogonadism (63.3%), adrenal hypofunction (59.5%), hypothyroidism (20.4%), and high (38.5%) and low (16.7%) prolactin levels. Preoperative imaging classified 93% of the tumors as macroadenomas. Their data confirmed elevated prevalence of mass effect and hypopituitarism in patients harboring NFPA.

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Fatemi N, Dusick JR, Mattozo C, McArthur DL, Cohan P, Boscardin J, Wang C, Swerdloff RS, Kelly DF (2008)[14]	Retrospective analysis of 223 patients with NFPAs out of 444 total with pituitary adenomas that underwent transsphenoidal resection over an 8-year period at a single institution. Those with previous sellar radiotherapy were excluded.	Diagnostic / II	Of 231 patients with endocrine-inactive adenomas, 194 (84%) had preoperative hormonal dysfunction, including 120 (54%) with "stalk compression" hyperprolactinemia.
Del Monte P, Foppiani L, Ruelle A, Andrioli G, Bandelloni R, Quilici P, Prete C, Palummeri E, Marugo A, Bernasconi D (2007)[23]	Retrospective study to evaluate multiple features, including the clinical presentation characteristics of non-functioning pituitary macroadenomas (NFPM) in elderly patients. Twenty-seven patients (65-81 years; 13 males and 14 females) with NFPM (20-45 mm in diameter) were studied.	Clinical Assessment / II	Endocrinological evaluation on diagnosis showed global anterior hypopituitarism in 33% and partial hypopituitarism in 37% of patients.

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Gussi IL, Young J, Baudin E, Bidart JM, Chanson P (2003)[36]	Prospective case-control study to assess the sensitivity of CgA measurement in sporadic pituitary adenomas. Serum CgA was measured using a solid-phase 2-site immunoradiometric assay based on monoclonal antibodies that bind to 2 distinct contiguous epitopes within the 145-245 region of CgA	Diagnostic / II	Twenty-seven patients (12 men [64.2 +/- 11.8 years]), including 7 premenopausal women (38.4 +/- 5.7 years), and 8 postmenopausal women (67.7 +/- 10.3 years)] with NFPA. Mean basal CgA concentration in 14 normal subjects was 80.2 ng/ml (SD: 31.7; range 19-124). A cut-off value for normal range was thus set at 125 ng/ml. Three out of 27 subjects with NFPA (11%) had elevated basal CgA levels (576, 143, and 241 ng/ml, respectively). Serum levels of CgA were not influenced by TRH in any of the NFPA subjects (including those 3 with increased basal levels). The authors concluded that CgA serum levels measurement are not a helpful marker for the clinical management of functioning and nonfunctioning pituitary adenomas.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Drange MR, Fram NR, Herman-Bonert V, Melmed S (2000)[13]	Retrospective registration of 371 patients (99 clinically nonfunctioning tumors [CNFTs]) with radiological, biochemical, and clinical evidence of pituitary tumors was performed. Analysis of this primarily specialist-referred population revealed a female predominance among CNFT (60%).	Diagnostic / II	Males had a significantly greater frequency of macroadenomas than females for CNFTs (92% vs 68%). Concurrent hyperprolactinemia was present in CNFT (47%).
Gsponer J, De Tribolet N, Deruaz JP, Janzer R, Uske A, Mirimanoff RO, Reymond MJ, Rey F, Temler E, Gaillard RC, Gomez F (1999)[19]	Retrospective study on 353 consecutive patients with the presumptive diagnosis of pituitary tumor investigated from January 1984 through December 1997 at University Hospital, Lausanne, Switzerland. Nonsecreting adenomas (NSAs) were the most frequent pituitary tumors (40%).	Diagnostic / II	For the differential diagnosis of hyperprolactinemia basal prolactin (PRL) levels above 85 micrograms/L in the absence of renal failure and PRL-enhancing drugs and a PRL increment of less than 30% after thyrotropin-releasing hormone (TRH) accurately ruled out functional hyperprolactinemia due to NSA.

Popovic V, Damjanovic S (1998)[34]	Paradoxical response of luteinizing hormone (LH,) follicle-stimulating hormone (FSH), and alpha-subunits (alpha-SU) to thyrotropin-releasing hormone (TRH) have previously been reported. This study assessed the in vivo responses of LH, FSH, and alpha-SU to TRH in 34 patients with clinically nonfunctioning pituitary tumors (NFT).	Diagnostic / II	Twenty-three clinically NFT were postoperatively analyzed by immunocytochemistry, and 21 stained positive for beta-FSH and/or beta-LH. Two patients with NFT had elevated basal circulating levels of FSH (41.5 IU/L) and thus were characterized as FSH-secreting adenomas. TRH in these patients increased LH from basal 1.6 IU/L to 32.6 IU/L. In other patients with NFT, circulating levels of glycoprotein peptides were not elevated. TRH induced significant rise of LH in 8 (23.5%), FSH in 5 (14.7%), and alpha-SU in 10 (29.4%) patients with NFT. Thus, a bolus dose of TRH elicited a notable increment in FSH, LH, or alpha-SU in 23 of 34 patients with NFT. The authors confirmed that most NFTs are capable of synthesizing gonadotropin hormones and subunits (beta-FSH, beta-LH) and that most patients responded by either FSH, LH, or alpha-SU secretion after TRH, independent of basal hormone levels.

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Vierhapper H (1998)[31]	The study included 33 patients with non-functioning pituitary macroadenomas prior to transsphenoidal adenomectomy. This study was conducted to evaluate whether stimulated concentrations of growth hormone (GH) are of practical use in establishing the diagnosis of acquired GH deficiency.	Prognostic / II	Patients with pituitary macroadenomas who needed substitution therapy for at least 1 additional pituitary hormone presented with lower ($P < .05$) GHRH-stimulated GH secretion (3.2 +/- 4.3 ng/ml) than the remaining patients with pituitary tumors (7.2 +/- 6.6 mg/ml).

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Chanson P, Pantel J, Young J, Couzinet B, Bidart JM, Schaison G (1997)[35]	Prospective study in normal subjects and 26 patients with NFPA to assess if the paradoxical free LH beta response to TRH may be a useful clinical tool for determining the gonadotropic nature of NFPA. The authors used a very specific and sensitive immunoradiometric assay (IRMA) for free LH beta measurement and another specific IRMA to check the absence of free CG beta.	Diagnostic / II	In patients with NFPA, LH beta hypersecretion was found basally and/or after stimulation with TRH in 3 of 16 men, 3 of 5 premenopausal women, and 1 of 5 postmenopausal women; ie, 7 of 26 patients (26%). In 3 of these 7 cases, alpha-subunit and/or FSH levels were also increased. The LH beta measurement was thus truly informative on the gonadotropic nature of NFPA in only 4 out of 26 cases (15%). Basal plasma levels of LH beta were undetectable in normal men and premenopausal women in the early follicular phase. In contrast, normal postmenopausal women had increased basal plasma, LH beta parallel to dimeric LH, and alpha-subunit levels. In healthy subjects, stimulation with GnRH elicited an increase in LH beta, while TRH was ineffective. The authors concluded that, using a very sensitive and specific IRMA, free LH beta measurement is rarely helpful for determining the gonadotropic nature of NFPA.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Beentjes JA, Tjeerdsma G, Sluiter WJ, Dullaart RP (1996)[32]	Prospective study on 34 patients (20 females and 14 males [median age 52 (23-77) years]) with untreated non-functioning pituitary macroadenomas evaluated preoperatively in a university hospital setting. The analysis included the peak GH to ITT and to 100 micrograms GHRH in relation to an elevated PRL level (>200 mIU/l for males and >600 mIU/l for females) as an indication of hypothalamic-pituitary dysregulation as well as in relation to other anterior pituitary hormone deficiencies. A peak GH <5 micrograms/l in either test indicated GH deficiency.	Diagnostic / II	In the whole group, the median peak GH to GHRH (3.6 [0.9-26.3] micrograms/l) was higher than to ITT (1.6 [0.2-7.8] micrograms/l; *P* < .001). This difference was seen only in 19 patients with concomitant hyperprolactinaemia (*P* < .001). When hyperprolactinaemia was present, an insufficient GH peak was demonstrated by ITT in 16 cases and by GHRH stimulation in 7 cases (*P* < .01). Peak GH to ITT was lower in 24 patients with, compared to 10 patients without, other hormonal deficiencies (1.4 [0.2-5.6] vs 3.0 [1.0-7.8] micrograms/l; *P* < .02) but was not related to elevated PRL. In contrast, GHRH-stimulated GH was higher in hyperprolactinaemic than in normoprolactinaemic patients (5.9 [1.6-26.3] vs 2.9 [0.9-5.4] micrograms/l; *P* < .001) and was not related to the presence of other pituitary hormone deficiencies. Basal GH was positively correlated with PRL (R(s) = 0.36; *P* < .05). The authors concluded that ITT and GHRH tests cannot be used interchangeably in diagnosing GH deficiency in patients with non-functioning pituitary macroadenoma and hyperprolactinaemia and that hyperprolactinaemia may be associated with a diminished somatostatin tone, leading to a higher basal and GHRH-stimulated GH without having an effect on peak GH to ITT.

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Tjeerdsma (1996)[17]	Prospective case series of 40 consecutively enrolled patients with NFPAs and reported baseline hyperprolactinemia in 50% of patients. Hyperprolactinemia was defined as serum prolactin .200 mIU/I and .600 mIU/I in women.	Diagnostic / II	Hyperprolactinemia was associated with additional anterior pituitary axis deficiencies.
Greenman et al (1995)[30]	A prospective case series of 26 patients with NFPAs were studied.	Diagnostic / II	Authors reported baseline hypogonadism in 78% of patients, adrenal insufficiency in 43%, and hypothyroidism in 23% of patients. Impaired adrenal function was documented in 9 of 21 patients. Before surgery, more than 1 pituitary hormone axis was involved in 56% of patients. After surgery, 35% of patients had more than 1 pituitary hormone axis impaired after surgery. Postoperatively, the authors reported hypogonadism in 46% of patients, adrenal insufficiency in 50%, and hypothyroidism in 12%.
Berkmann et al (2012)[21]	A retrospective observational study at a single institution in Switzerland. A total of 182 patients who underwent surgical intervention for pituitary lesions were included. One hundred fourteen of 182 patients (63%) had NFPAs.	Clinical Assessment / II	Of 114 patients with NFPAs, 83 presented with preoperative hypopituitarism.

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Chen et al (2011)[26]	A prospective observational study of 385 patients with NFPAs who underwent surgical intervention for resection of tumor. Mean follow-up was 5.5+/-1.4 years. Hypopituitarism at baseline was analyzed.	Clinical Assessment / II	In 385 patients analyzed before and after endoscope-assisted transsphenoidal resection of tumor, preoperative hypopituitarism was noted as follows: hypothyroidism 35.8%, hypogonadism 41%, hypoprolactinemia 17.9%, GH deficiency 61%.
Nomikos et al (2004)[16]	Retrospective study on 822 patients who underwent primary surgery in a single center: 721 cases had complete set of endocrinological data.	Clinical Assessment / II	Preoperative hypopituitarism found in 561 (85%) and 53 (86.3%) of the patients belonging to the transsphenoidal and the transcranial groups, respectively: 163 (31%) of the patients had secondary adrenal deficiency, 463 (76.6%) had hypogonadism, and 105 (19.1%) were hypothyroid. Preoperatively, prolactin levels were mildly elevated in 167 patients (25.3%).
Marazuela M, Astigarraga B, Vicente A, Estrada J, Cuerda C, García-Uría J, Lucas T (1994)[24]	Retrospective study in 35 patients with non-functioning pituitary adenomas studied before and after transsphenoidal surgery in a single center.	Clinical Assessment / II	Preoperatively, 24 patients (69%) had abnormal pituitary function, 24 (69%) had hypogonadism, 7 (20%) adrenal insufficiency, 8 (23%) hypothyroidism, and 2 (6%) panhypopituitarism.

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Karavitaki et al (2006)[15]	Retrospective analysis of 226 patients with histological proven NFAs. Median age 55 years (18-88), 65% men, 41 patients on medications that can influence prolactin levels.	Diagnostic / II	Hyperprolactinaemia was found in 38.5% (87/226) of the patients. The median serum PRL values in the total group were 386 mU/l (range 16-3257) (males: median 299 mU/l, range 16-1560; females: median 572 mU/l, range 20-3257) and, in those not taking drugs capable of increasing serum PRL, 363 mU/l (range 16-2565) (males: median 299 mU/l, range 16-1560; females: median 572 mU/l, range 20-2565). Serum PRL <2000 mU/l was found in 98.7% (223/226) of the total group and in 99.5% (184/185) of those not taking drugs. Among the 3 subjects with serum PRL >2000 mU/l, 2 were on estrogen treatment. The authors concluded that a serum PRL >2000 mU/l is almost never encountered in nonfunctioning pituitary macroadenomas.

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Webb et al (1999)[22]	Retrospective analysis of 234 patients with pituitary adenomas (56 NFA) treated with transsphenoidal resection. Preoperative anterior pituitary function was evaluated: PRL, free T4, TSH, cortisol, ACTH or ACTH stimulation test, GH stimulation after ITT. Hypogonadism was defined by low testosterone, low LH and FSH in men, inappropriately low FSH and LH in postmenopausal women, or low estradiol with low/low normal LH and FSH in premenopausal women with menstrual abnormalities.	Clinical Assessment / II	Of 56 patients with NFPAs, 52% had some element of hypopituitarism preoperatively.
Comtois R, Beauregard H, Somma M, Serri O, Aris-Jilwan N, Hardy J (1991)[11]	Retrospective study on 126 patients who underwent transsphenoidal surgery for primary treatment of NFA in a single center from 1962 to 1987. Data on preoperative hormonal work-up was collected. There were 73 male and 53 female patients (mean age, 50 +/- 12 years).	Clinical Assessment / II	Endocrine evaluation revealed the presence of hypogonadism in 75% (87 of 115), adrenal insufficiency in 36% (46 of 126), and hypothyroidism in 18% (21 of 122). Plasma prolactin was increased in 65% (56 of 86) with a mean level of 39 +/- 14 micrograms/l (normal, 3 to 20 micrograms/l).

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Arafah et al (1986)[9]	Prospective study of 26 patients with large nonfunctioning pituitary adenomas before and 2-3 months after transsphenoidal adenomectomy. Basal serum PRL, GH, TSH, LH, FSH, and ACTH levels were measured, and dynamic studies of their secretion were also analyzed.	Clinical Assessment / II	Preoperatively, GH deficiency was found in all 26 patients (100%), hypogonadism in 25 patients (96%), hypothyroidism in 21 patients (81%), and adrenal insufficiency in 16 patients (62%). Serum PRL levels were low (1.5-4 ng/ml) in 5 patients, normal (5-20 ng/ml) in 9 patients, and mildly elevated (21-53 ng/ml) in the remaining 12 patients.
Colao A, Cerbone G, Cappabianca P, Ferone D, Alfieri A, Di Salle F, Faggiano A, Merola B, de Divitiis E, Lombardi G (1998)[28]	Retrospective study in 84 patients with clinical nonfunctioning pituitary adenomas (NFPA) subjected to 1-10 years of follow-up. Hormonal evaluation was done before and after surgery.	Clinical Assessment / II	At diagnosis, deficiency of GH, TSH, ACTH, FSH, LH, and ADH was documented in 55, 7, 19, 47, and 6 patients, respectively.

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Dekkers OM, Pereira AM, Roelfsema F, Voormolen JH, Neelis KJ, Schroijen MA, Smit JW, Romijn JA (2006)[25]	Retrospective follow-up study of 109 consecutive patients (age 56 +/- 13 years) operated for NFMA between 1992 and 2004.	Clinical Assessment / II	Preoperatively, 77% of patients had GH deficiency, 75% hypogonadism, 53% adrenal insufficiency, 43% hypothyroidism; overall, 29% patients had panhypopituitarism.
Tominaga A, Uozumi T, Arita K, Kurisu K, Yano T, Hirohata T (1995)[18]	Retrospective study of 33 patients whose anterior pituitary function was evaluated by provocative tests such as insulin induced hypoglycemia, thyrotropin releasing hormone administration test, and luteinizing hormone releasing hormone administration test.	Clinical Assessment / II	Preoperative endocrinological evaluation showed impaired secretion of GH in 30 out of 31 patients (97%), LH in 16 patients (52%), ACTH in 15 patients (48%), FSH in 13 patients (42%), TSH in 6 patients (19%), and PRL in two patients (6.5%). Hyperprolactinemia was found in 13 patients (42%).

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Wichers-Rother et al (2004)[27]	Retrospective analysis of 155 patients with NFPA to evaluate anterior pituitary function before and after transsphenoidal and/or transcranial surgery. Thirty patients harbored a macroadenoma, 109 underwent transsphenoidal surgery (group 1), and 21 underwent transcranial surgery (group 2). Twenty-five patients presented a microadenoma (transsphenoidal surgery, group 3). Endocrine studies included basal serum levels and dynamic testing of anterior pituitary partial function.	Clinical Assessment / II	Preoperatively, in group 1, 2, and 3, GH deficiency was found in 85%, 90%, and 80%; gonadal dysfunction in 61%, 57%, and 24%; adrenal insufficiency in 31%, 38%, and 28%; and hypothyroidism in 32%, 38%, and 12%.
Ebersold MJ, Quast LM, Laws ER Jr, Scheithauer B, Randall RV (1986)[29]	One hundred patients who had undergone a transsphenoidal procedure in a single center.	Clinical Assessment / II	36% hypogoandism, 17% adrenal insufficiency, 32% hypothyroidism.

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Behan LA, O'Sullivan EP, Glynn N, Woods C, Crowley RK, Tun TK, Smith D, Thompson CJ, Agha A (2013)[10]	Retrospective study. Clinical, biochemical, histopathological, and radiological data were recorded and analyzed in 250 subjects with NFPA.	Diagnostic / II	Of 250 patients, 44.8% were hyperprolactinemic at presentation, and out of these patients, 73.2% had PRL <1000 mIU/l and 24.1% had PRL between 1000 and 1999 mIU/l. 55.3% of patients with hyperprolactinemia were female. 2.7% (3 females, 2 of them pregnant) had PRL >2000 mIU/l, 94.3 ng/ml). No male subjects and no subjects with an intrasellar macroadenoma had serum PRL >1000 mIU/l (47.2 ng/ml). Forty-three subjects taking medications known to raise PRL did not have overall higher PRL levels.