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Supplemental Results

MRI findings

Among the 672 patients with a pituitary macroadenoma, tumor size was similar in men (15±7.5 x 16±8 x 14±7.2 mm for the vertical, lateral and antero-posterior diameters, respectively) and women (15±7 x 15±7 x 14±6.5 mm; p=ns), as was tumor volume calculated with the elliptic formula (4.196±2.561 versus 3.204±2.372 mm³; p=ns). Pituitary tumor diameters correlated positively with GH (r=0.22, p<0.0001) and xULN IGF-I (r=0.42, p=0.0006) levels at diagnosis, and negatively with age (r=0.28, p<0.0001). Age at diagnosis correlated negatively with the vertical (r=0.27), lateral (r=0.26) and antero-posterior (r=0.18) pituitary tumor diameters (p<.001 for all). Macroadenomas extended laterally (54.4%), upwards (34.5%) and downwards (27%). Tumor extension did not differ according to gender or age. The percentage of patients with macroadenomas did not change significantly over time (71% before 2000, 78% between 2000 and 2004, and 75% after 2005; p=ns).

Biochemical control
Average GH levels in the entire cohort fell from 17.8 ng/mL (interquartile range, 7.1-41) at inclusion to 1.8 ng/mL (0.8-4) at the last visit (excluding patients receiving the GH receptor antagonist pegvisomant). Mean IGF-I levels fell from 900 (624-1158) to 216 (159-312) ng/mL, respectively, and from 2.62 (1.66-3.66) to 0.77 (0.55-1.04) ULN when adjusted for age and gender (Supplemental Figure 3).

Disease control had been achieved at the last visit in 75% of the 964 patients with available IGF-I values. The last available x ULN IGF-I was not different between centers with high (more or equal 50 inclusions) or low (<50) patients caseload (92±65 vs 112±93 x ULN, respectively).

Disease control defined as mean GH <1 ng/mL was achieved in 331 (51%) of the 649 patients with available values. Among the 633 patients for whom both GH and IGF-I levels were available at the last visit, 45% of them had both normal GH and IGF-I levels (concordantly normalized), 27% had normal IGF-I but elevated GH levels (discordant), and 7% had normal GH but elevated IGF-I levels (discordant). Both GH and IGF-I levels remained elevated in 21% of cases (concordantly uncontrolled, see Supplemental Figure 4A). When disease control was defined as mean GH <2 ng/mL, 59% of patients had concordantly normalized GH and IGF-I levels, 13% had normal IGF-I but elevated GH levels, 11% had normal GH but elevated IGF-I levels, and 17% had concordantly uncontrolled GH and IGF-I levels.

When disease control was defined as a nadir GH <0.4 ng/mL in the OGTT suppression test (261 patients), it was achieved in 52.5% of cases for both GH and IGF-I (concordantly normalized), while 29.5% of patients had normal IGF-I but elevated GH levels, 5% had normal GH but elevated IGF-I levels (discordant), and 13% had elevated IGF-I and GH levels (concordantly uncontrolled, see Supplemental Figure 4B). When disease control was defined as a post-OGTT GH nadir <1 ng/mL, concordantly normalized in 70.5% of patients, while 9% of patients had normal IGF-I but
unsuppressed GH, 11.5% had suppressed GH but elevated IGF-I (discordant), and 9% had concordantly uncontrolled GH and IGF-I.

**Treatment outcomes**

A total of 47% of patients for whom postoperative IGF-I was available, normalized their levels after surgery. However, when including only patients for whom IGF-I levels were assessed at least 3 months after surgery, 48% of patients normalized their levels. This rate did not change when comparing centers with high (44.8%) to those with low (48.9%) patients caseload. The post-surgical success rate was lower in patients with macroadenomas than in patients with microadenomas, whether centers had high (42 vs 61%, p=0.0095) or low (44 vs 75%, p=0.0036) patients caseload. IGF-I levels normalized in a further 11% of patients for whom a subsequent biochemical assessment was available. On the other hand, recurrence was noted in 13% of patients initially considered as cured.

**Respiratory comorbidities**

239 patients were diagnosed with obstructive sleep apnea, by polysomnography in 123 cases and by nighttime oxymetry or clinical interview alone in the remaining cases. At the last visit, OSA resolution has been registered in only 8 patients, whereas 8 newly incident cases occurred during the follow-up. Logistic regression analysis showed that IGF-I levels at baseline, expressed as x ULN, correlated with respiratory complications (p= .023) and OSA (p= .027). This statistical significance disappeared after adjustment for age, BMI, or both. Respiratory failure was diagnosed in 29 patients.

**Rheumatologic comorbidities**

Among the 923 patients for whom this information was available, 348 patients had arthralgia and 272 patients the carpal tunnel syndrome. At the last visit, nineteen patients underwent reversal of
rheumatologic comorbidities. On the other hand, nine cases newly occurred during the follow-up.

Hip osteoarthropathy was diagnosed in 8% of patients. Arthralgias and the carpal tunnel syndrome correlated positively with ULN IGF-I levels at baseline (p < 0.01), but not after adjustment for age, sex and BMI.

**Pituitary function**

The prevalence of gonadotrope failure was higher in men (30.7%) than in women (15%, p<.001 Chi-square test). Elevated ULN IGF-I levels at baseline correlated with pituitary defects of any axis (p= .038) and with gonadotrope deficiency (p= .021). Elevated GH levels correlated positively with the existence of any pituitary defect (p<.0001), and with gonadotrope (p<.0001), corticotrope (p= .0001) and thyrotrope (p=.0002) deficiency.