

SCIENTIFIC LETTER

Long-term effect of combined therapy with somatostatin analogs and dopamine agonists as a primary treatment in a non-functioning invasive pituitary macroadenoma



Efecto terapéutico a largo plazo de los analógos de somatostatina y agonistas dopaminérgicos como tratamiento médico primario en un macroadenoma hipofisario no funcionante invasivo

Pituitary adenoma (PA) constitutes 15% of intracranial tumors. Non-functioning PA (NFWPA) is the second most common type of PA after prolactinoma, with a prevalence of 22.2 cases/100,000 inhabitants.¹ In most cases, NFWPA is a macroadenoma (≥ 1 cm) whose clinical presentation is variable; from an incidental oligosymptomatic finding to a true giant PA with great local involvement of neighboring structures and different degrees of hypopituitarism.² Its clinical management varies depending on the size of the tumor, its growth over time and neuro-ophthalmic involvement. Surgical treatment followed by radiotherapy of the remnant or tumor recurrence is the usual treatment. The clinical experience with medical treatment with somatostatin analogs (SSA) and dopamine agonists (DA) as a primary treatment in these tumors is poorly defined.

A 46-year-old man was referred to us for assessment of pituitary tumor discovered in a cranial CT during the study of headache in the last 5–6 months. Clinically, the patient did not show symptoms of adenohypophyseal hypo-hyperfunction or diabetes insipidus. No galactorrhea or erectile dysfunction, and libido was preserved. Hormonal evaluation showed central hypogonadism [FSH 2.3 mIU/ml (NR, 1.4–18), LH 1.5 mIU/ml (1.5–9.3), testosterone 93.9 ng/dl (241 – 827)], and mild hyperprolactinemia [PRL 49.1 ng/ml (2.2–17.7), PRL after dilution 47.8 ng/ml]. The rest of the pituitary function was normal [TSH 2.05 μ IU/ml (0.35–5.0), free T4 1.09 ng/dl (0.7–1.98), ACTH 56.3 pg/ml (9.0–55.0), cortisol 13.6 μ g/dl (4.3–22.4), urinary free cortisol 16 μ g/24h (11.0–71.0), Nugent test: cortisol 0.8 μ g/dl, GH 0.8 ng/ml (4.3–6.3), and IGF-I 134 ng/ml (55.0–420.0)]. Pituitary MRI confirmed the presence of an invasive pituitary tumor of 2.0 \times 1.7 \times 3.0 cm with suprasellar extension with greater involvement of the right side, extending to both cavernous sinuses and encompassing the right and partially left carotid (Fig. 1). The campimetric study of the visual fields was normal. A

^{99m}Tc-EDDA/HYNIC-Tyr3-Octreotide (tektrotyd) scintigraphy revealed a hypercaptant lesion at pituitary level (Fig. 1). With the clinical diagnosis of invasive non-functioning pituitary macroadenoma associated with mild hyperprolactinemia, due to probable compression of the pituitary stalk, and central hypogonadism, he started therapy with lanreotide autogel 120 mg/month sc and oral cabergoline 0.5 mg/week, and was referred to the Neurosurgery Department for surgical treatment of the PA. Shortly after starting medical treatment, the patient showed a marked clinical improvement of headaches, without visual disturbances. A new pituitary MRI performed 3 months after starting medical treatment showed a marked reduction in pituitary adenoma size (1.2 \times 1.5 \times 2.5 cm) (Fig. 1). Due to the excellent clinical and radiological evolution, it was decided to postpone surgery. At 6 months after starting medical treatment, the patient referred notable clinical improvement of headaches without visual disturbances, the adenohypophyseal function was controlled (testosterone 496.10 ng/dl and PRL 0.5 ng/ml) and pituitary MRI showed marked reduction of the macroadenoma size with respect to the previous MRI (Fig. 1). From that moment the patient was treated with lanreotide autogel 120 mg/month sc and oral cabergoline 0.25 mg/week. A year and a half after starting treatment, pituitary function remained controlled (testosterone 418 ng/dl and PRL 0.5 ng/ml) and tumor size remained stable with respect to the last pituitary MRI performed at sixth month.

NFWPA is around 25–35% of pituitary tumors, being most of them gonadotropinomas, which account for as many as 40–50% of all pituitary macroadenomas.³ At diagnosis, most NFWPAs are macroadenomas and, on many occasions, they are incidentally diagnosed.² Surgery is the treatment of choice for symptomatic (headache, visual disturbances and neurological involvement) NFWPAs, those associated with pituitary apoplexy and those that show growth during the surveillance. However, complete surgical resection, especially in invasive adenomas (Knosp grades 3–4) is exceptionally achieved. For this reason and, as a complementary treatment to a debulking surgery, radiotherapy is usually used to control the tumor remnant or its recurrence.⁴ Radiotherapy achieves an excellent long-term local tumor control but at the expense of a high rate of hypopituitarism.

As occurs with prolactinomas, where DAs constitute the first-line therapy, NFWPAs also express dopamine D2 receptors (D2R). D2R expression has been reported in about 35–40% of NFWPAs and DAs (bromocriptine and cabergoline) have been shown to decrease gonadotropin and alpha-subunit secretion in gonadotroph adenomas.^{5–7} Therefore, DAs could have

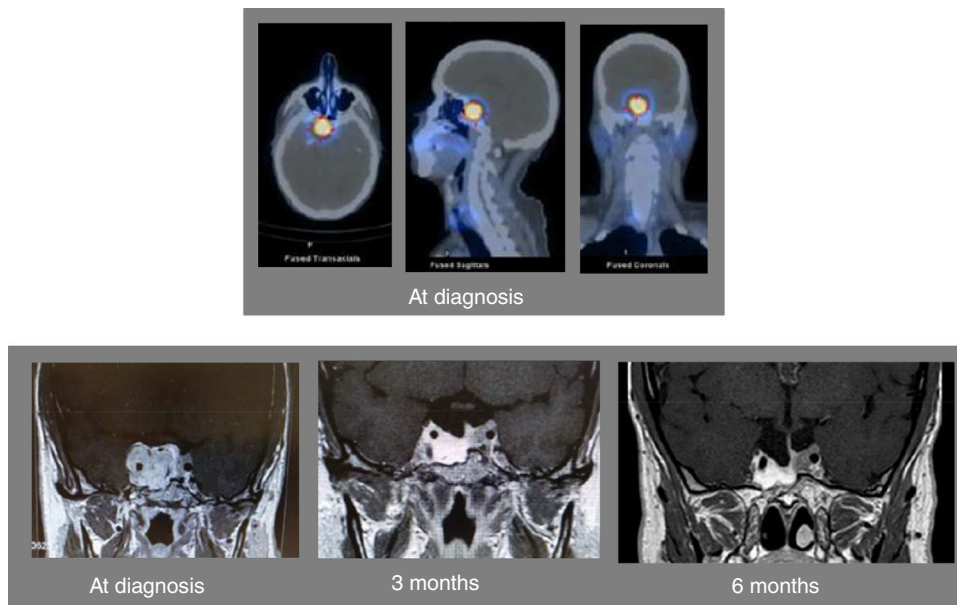


Figure 1 Axial (left above), sagittal (center above), and sagittal (right above) images of the SPECT-TC with ^{99m}Tc -EDDA/HYNIC-Tyr3-Octreotide (tektrotyd) scintigraphy at diagnosis showing a hypercaptant lesion at the level of the pituitary tumor. Pituitary MRI at diagnosis showing an invasive pituitary tumor of $2.0 \times 1.7 \times 3.0$ cm with suprasellar extension with greater involvement of the right side, extending to both cavernous sinuses and encompassing the right and partially left carotid (left down). Pituitary MRI 3 months (center down) and 6 months (right down) after starting combined therapy with lanreotide and cabergoline.

a therapeutic role in the medical management of NFPAs. In fact, in these patients, pooled results have shown a reduction of tumor size and stabilization of disease in 30% and 58% of patients, respectively.⁸

On the other hand, NFPAs can also express somatostatin receptors (SSTRs),⁹ although its clinical relevance has not been fully defined. The finding of significant expression of SSTR type 2 (SSTR2) and type 5 (SSTR5) has suggested a possible therapeutic role regarding the use of SST analogs in preventing tumor recurrence in NFPAs.¹⁰ SSA as primary medical therapy for NFPAs has shown low tumor response rates (12–40%),¹¹ however the combination therapy with DA and SSA can increase tumor response rate [mean reduction in tumor volume of $30 \pm 4\%$ (18–46%) after 6 months of combination therapy with octreotide and cabergoline] in 60% of NFPA patients.¹² SSTRs and D2R may have additive effects on cell proliferation in pituitary adenomas thought interaction by heterodimerization as shown for SSTR1-SSTR5, SSTR5-D2R, SSTR2-SSTR3, and SSTR2-D2R.⁸ In fact, SSA and cabergoline are usually used after surgery in invasive NFPA.

In our patient, the long-term clinical management with combined medical treatment with SSA and DA was encouraged for several facts: (1) the positive tumor uptake in scintigraphy with ^{99m}Tc -tektrotyd that was compatible with high SSTR expression by the tumor; (2) the spectacular and rapid clinical response of headache to medical treatment associated with good tolerance; (3) the adequate control of hyperprolactinemia and hypogonadism with cabergoline; (4) the low probability of complete surgical resection due to the high degree of invasiveness of the tumor (Knosp grades 3–4); and (5) the rapid (3 months) and striking response in terms of tumor size reduction (Fig. 1).

In summary, our clinical case suggests that those patients with large and invasive NFPAs without neuro-

ophthalmological involvement and little likelihood of complete surgical resection, that are associated with mild hyperprolactinemia and positive tumor uptake in SSTR scintigraphy, combined treatment with DA and SSA could be considered as an initial therapeutic alternative to surgical treatment.

Informed consent

The patient signed the consent for the publication of the clinical case.

Conflicts of interest

The authors have no conflict of interest and financial support in relation to the present manuscript.

References

1. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol (Oxf)*. 2010;72:377–82.
2. Iglesias P, Arcano K, Trivino V, García-Sancho P, Díez JJ, Villabona C, et al. Prevalence, clinical features, and natural history of incidental clinically non-functioning pituitary adenomas. *Horm Metab Res*. 2017;49:654–9.
3. Chaidarun SS, Klibanski A. Gonadotropinomas. *Semin Reprod Med*. 2002;20:339–48.
4. Minniti G, Flickinger J, Tolu B, Paolini S. Management of nonfunctioning pituitary tumors: radiotherapy. *Pituitary*. 2018;21:154–61.
5. Wang Y, Li J, Tohti M, Hu Y, Wang S, Li W, et al. The expression profile of dopamine D2 receptor MGMT and VEGF in different histological subtypes of pituitary adenomas: a study of 197 cases

- and indications for the medical therapy. *J Exp Clin Cancer Res*. 2014;33(56), 014-0056-y.
6. Kwekkeboom DJ, Hofland LJ, van Koetsveld PM, Singh R, van den Berge JH, Lamberts SW. Bromocriptine increasingly suppresses the in vitro gonadotropin and alpha-subunit release from pituitary adenomas during long term culture. *J Clin Endocrinol Metab*. 1990;71:718–24.
 7. Giusti M, Bocca L, Florio T, Foppiani L, Corsaro A, Auriati L, et al. Cabergoline modulation of alpha-subunits and FSH secretion in a gonadotroph adenoma. *J Endocrinol Invest*. 2000;23:463–6.
 8. Saveanu A, Jaquet P, Brue T, Barlier A. Relevance of coexpression of somatostatin and dopamine D2 receptors in pituitary adenomas. *Mol Cell Endocrinol*. 2008;286:206–13.
 9. Cooper O, Greenman Y. Dopamine agonists for pituitary adenomas. *Front Endocrinol (Lausanne)*. 2018;9:469.
 10. Ramirez C, Cheng S, Vargas G, Asa SL, Ezzat S, González B, et al. Expression of Ki-67, PTTG1, FGFR4, and SSTR 2, 3, and 5 in nonfunctioning pituitary adenomas: a high throughput TMA, immunohistochemical study. *J Clin Endocrinol Metab*. 2012;97:1745–51.
 11. Lucas JW, Bodach ME, Tumialan LM, Oyesiku NM, Patil CG, Litvack Z, et al. Congress of neurological surgeons systematic review and evidence-based guideline on primary management of patients with nonfunctioning pituitary adenomas. *Neurosurgery*. 2016;79:E533–5.
 12. Andersen M, Bjerre P, Schrøder HD, Edal A, Høilund-Carlson PF, Pedersen PH, et al. In vivo secretory potential and the effect of combination therapy with octreotide and cabergoline in patients with clinically non-functioning pituitary adenomas. *Clin Endocrinol (Oxf)*. 2001;54:23–30.

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Absceso hipotálamo hipofisario como complicación de sinusitis aguda: caso clínico y evolución con tratamiento conservador



Hypothalamic-pituitary abscess as a complication of acute sinusitis: A case report and evolution with conservative management

El absceso hipofisario (AH) es una lesión hipofisaria poco frecuente. Podríamos sospechar este diagnóstico ante un cuadro de hipopituitarismo, una imagen de RMN hipofisaria sugerente y una historia de meningitis, sinusitis o cirugía craneal recientes. Presentamos el caso de un paciente afecto de AH que evolucionó favorablemente con tratamiento médico.

Un hombre de 55 años de edad, fumador, consumidor de alcohol y cocaína inhalada, con antecedentes de meningitis en la infancia y cólicos nefríticos de repetición por los que el paciente tenía como costumbre beber 4-5 l de agua al día. Presentó cefalea frontal de 2 meses de evolución, siendo diagnosticado por TAC de sinusitis aguda maxilar, etmoidal y esfenoidal. Recibió tratamiento antibiótico presentando empeoramiento clínico y fue llevado a urgencias por deterioro agudo del nivel de consciencia, cefalea y fiebre. Mediante LCR y TAC craneal se diagnosticó meningoencefalitis con edema cerebral y signos incipientes de herniación uncal. Ingresó en la Unidad de Cuidados Intensivos durante 7 días, recibiendo antibioterapia, derivación ventricular externa y dexametasona 4 mg/8 h (5 días) presentando buena respuesta inicial, pero con persistencia de fiebre. A los 3 días del alta de la UCI y 4 o 5 días después de suspender el tratamiento corticoideo presentó hipotensión, náuseas y vómitos. Los hallazgos analíticos más relevantes fueron ACTH 19,9 pg/ml (4,7-48 pg/ml), cortisol

5,37 mcg/dl (6-19,4 mg/dl), TSH 0,52 mU/l (0,4-4 mU/l), T3 1,18 pg/ml (1,8-4,6 pg/ml), T4 0,55 ng/dL (0,7-1,8 ng/dL), LH < 0,1 mUI/ml (1,7-8,6 mUI/ml), FSH 1,19 mUI/ml (1,5-12,4 mUI/ml), testosterona 0,03 mcg/l (2,8-8 mcg/l).

La RMN mostró una colección quística en el hipotálamo con restricción de la difusión de 12 × 9 × 11 mm en continuidad con otra imagen en la hipófisis de 14 × 12 × 8 mm, hallazgos compatibles con absceso hipotálamo hipofisario (figs. 1. A y B).

Se diagnosticó panhipopituitarismo secundario a absceso infundíbulo hipofisario. Tras instaurar tratamiento sustitutivo con corticoides y levotiroxina, y coincidiendo con la ingesta libre de agua, a la que el paciente estaba acostumbrado, se manifestó cuadro de poliuria de hasta 11 l. Se realizó prueba de restricción hídrica que fue compatible con diabetes insípida (DI) central (osmolaridad urinaria basal 103 mOsm/kg [300-1.000 mOsm/kg], tras restricción hídrica 272 mOsm/kg y postadministración de desmopresina 402 mOsm/kg) y se inició tratamiento con desmopresina.

Los cultivos de LCR y sangre fueron negativos; en el cultivo de pus de los senos paranasales creció *Staphylococcus epidermidis*, *Streptococcus parasanguinis* y *Streptococcus constellatus*. Se ajustó antibiótico que mantuvo 6 semanas.

El paciente continúa seguimiento en endocrinología; a los 6 meses del inicio del cuadro se ha recuperado el déficit de ACTH y ADH. En la RMN del primer mes se había resuelto el absceso hipotalámico y al sexto mes el absceso hipofisario (figs. 1C y D).

Los AH son lesiones selares poco frecuentes (< 1% de todas las lesiones hipofisarias), pero con elevada mortalidad¹⁻³.

Pueden clasificarse de acuerdo a su etiología en AH primarios (70%) —ocurren en una glándula previamente sana— y secundarios (30%), que surgen de lesiones preexistentes, siendo el adenoma hipofisario el más común, seguido del quiste de Rathke, craneofaringioma y linfoma^{1,3-5}.