Pituitary MRI Features in Acromegaly Resulting From Ectopic GHRH Secretion From a Neuroendocrine Tumor: Analysis of 30 Cases

Iulia Potorac,[1] Jean-François Bonneville,[1,2] Adrian F. Daly,[1] Wouter de Herder,[3] Patricia Fainstein-Day,[4] Philippe Chanson,[5] Marta Korbonits,[6] Fernando Cordido,[7] Elisa Baranski Lamback,[8] Mohamed Abid,[9] Véronique Raverot,[10] Gerald Raverot,[11] Emma Anda Apiñániz,[12] Philippe Caron,[13] Helene Du Boullay,[14] Martin Bidlingmaier,[15] Marek Bolanowski,[16] Marie Laloi-Michelin,[17] Francoise Borson-Chazot,[18] Olivier Chabre,[19] Sophie Christin-Maitre,[20] Claire Briet,[21] Gonzalo Diaz-Soto,[22] Fabrice Bonneville,[23] Frederic Castinetti,[24] Mônica R. Gadelha,[8] Nathalie Oliveira Santana,[25] Maria Stelmachowska-Banaś,[26] Tomas Gudbjartsson,[27] Roció Villar-Taibo,[28] Taiba Zornitzki,[29] Luaba Tshibanda,[2] Patrick Petrossians,[1] and Albert Beckers[1]

[1]Departments of Endocrinology, Centre Hospitalier de Liège, Université de Liège, Domaine Universitaire du Sart Tilman, 4000 Liège, Belgium

[2]Medical Imaging, Centre Hospitalier de Liège, Université de Liège, Domaine Universitaire du Sart Tilman, 4000 Liège, Belgium

[3]Department of Internal Medicine, Section of Endocrinology, Erasmus University Medical Center, 3015 GD, Rotterdam, The Netherlands

[4]Department of Endocrinology, Hospital Italiano de Buenos Aires, 1199, Buenos Aires, Argentina

[5]Université Paris-Saclay, Inserm, Physiologie et Physiopathologie Endocriniennes, Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, Service d'Endocrinologie et des Maladies de la Reproduction, Centre de Référence des Maladies Rares de l'Hypophyse HYPO, 94270 Le Kremlin-Bicêtre, France

[6]Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London E1 4NS, United Kingdom

[7]Department of Endocrinology, University Hospital A Coruña, 15006 A Coruña, Spain

[8]Neuroendocrinology Research Center/Endocrinology Division, Medical School and Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, 21941-617 Rio de Janeiro, Brazil

[9]Department of Endocrinology, Hedi Chaker Hospital, 3000 Sfax, Tunis

[10]Biochemistry Laboratory Department, Groupement Hospitalier Est, Hospices Civils de Lyon, 69002 Lyon, France

[11]*Fédération d'Endocrinologie, Centre de Référence des Maladies Rares Hypophysaires HYPO, Groupement Hospitalier Est, Hospices Civils de Lyon, 69002 Lyon, France*

[12]*Department of Endocrinology and Nutrition, Complejo Hospitalario de Navarra, 31008 Pamplona, Spain*

[13]*Service d'Endocrinologie et Maladies Métaboliques, Centre Hospitalier Universitaire de Toulouse, 31300 Toulouse, France*

[14]*Department of Endocrinology, General Hospital of Chambéry, 73000 Chambéry, France*

[15]*Department for Endocrinology, Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-University, 80539 Munich, Germany*

[16]*Department of Endocrinology, Diabetes and Isotope Therapy, Wroclaw Medical University, 50-367 Wroclaw, Poland*

[17]*Department of Diabetes and Endocrinology, Lariboisière Hospital, 75010 Paris, France*

[18]*Hospices Civils de Lyon, Fédération d'Endocrinologie, Université Claude Bernard Lyon 1, 69002 Lyon, France*

[19]*Service d'Endocrinologie, Centre Hospitalier Universitaire de Grenoble, 38700 La Tronche, France*

[20]*Department of Endocrinology, Hôpital St Antoine, AP-HP, Sorbonne University, 75012 Paris, France*

[21]*Service d'endocrinologie, diabétologie et nutrition, CHU d'Angers, 49100 Angers, France*

[22]*Servicio de Endocrinología y Nutrición, Hospital Clínico Universitario de Valladolid, 47003 Valladolid, Spain*

[23]*Department of Neuroradiology, University Hospital Purpan, 31300 Toulouse, France*

[24]*Department of Endocrinology, Aix Marseille Université, 13007 Marseille, France*

[25]*Laboratório de Endocrinologia Celular e Molecular (LIM25), Hospital das Clínicas da Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP 05403-000, Brasil*

[26]*Department of Endocrinology, The Centre of Postgraduate Medical Education, 01-813 Warsaw, Poland*

[27]*Department of Cardiothoracic Surgery, Landspitali University Hospital, Faculty of Medicine, University of Iceland, 101 Reykjavik, Iceland*

[28]*Endocrinology and Nutrition Department, Complejo Hospitalario Universitario de Santiago de Compostela, 15706 Santiago de Compostela, Spain*

[29]*Diabetes, Endocrinology and Metabolic Disease Institute, Kaplan Medical Center, Hebrew University Medical School, Rehovot 76100, Israel*

Correspondence: Albert Beckers, MD, PhD, Departments of Endocrinology, Centre Hospitalier de Liège, Université de Liège, Domaine Universitaire du Sart Bonneville MD, PhD, Departments of Endocrinology, Centre Hospitalier de u Sart Tilman, 4000 Liège, Belgium. Email: bonnevillejf@gmail.com.

Abstract

Context. Ectopic acromegaly is a consequence of rare neuroendocrine tumors (NETs) that secrete GHRH. This abnormal GHRH secretion drives GH and IGF-1 excess, with a clinical presentation similar to classical pituitary acromegaly. Identifying the underlying cause for the GH hypersecretion in the setting of ectopic GHRH excess is, however, essential for proper management both of acromegaly and the NET. Owing to the rarity of NETs, the imaging characteristics of the pituitary in ectopic acromegaly have not been analyzed in depth in a large series.

Objective. Characterize pituitary magnetic resonance imaging (MRI) features at baseline and after NET treatment in patients with ectopic acromegaly.

Design. Multicenter, international, retrospective.

Setting. Tertiary referral pituitary centers.

Patients. Thirty ectopic acromegaly patients having GHRH hypersecretion.

Intervention. None.

Main outcome measure. MRI characteristics of pituitary gland, particularly T2-weighted signal.

Results. In 30 patients with ectopic GHRH-induced acromegaly, we found that most patients had hyperplastic pituitaries. Hyperplasia was usually moderate but was occasionally subtle, with only small volume increases compared with normal ranges for age and sex. T2-weighted signal was hypointense in most patients, especially in those with hyperplastic pituitaries. After treatment of the NET, pituitary size diminished and T2-weighted signal tended to normalize.

Conclusions. This comprehensive study of pituitary MRI characteristics in ectopic acromegaly underlines the utility of performing T2-weighted sequences in the MRI evaluation of patients with acromegaly as an additional tool that can help to establish the correct diagnosis.

Keywords

Acromegaly, ectopic, MRI, GHRH, T2-hypointense, pituitary, neuroendocrine tumor

Abbreviations

CV, coefficient of variation; **MEN1,** multiple endocrine neoplasia type 1; **MRI,** magnetic resonance imaging; **NET,** neuroendocrine tumor; **SRL,** somatostatin receptor ligand; **T2W,** T2-weighted

Acromegaly is a rare endocrine disorder with an estimated prevalence of 10.5 cases per 100 000 individuals (1). It is usually the result of GH hypersecretion from a pituitary adenoma. Less than 1% of cases of acromegaly are secondary to ectopic secretion of GHRH, usually from a bronchial or pancreatic neuroendocrine tumor (NET), although other sources of abnormal GHRH secretion have been described (eg, hypothalamic gangliocytomas (2)).

The rare nature of ectopic acromegaly can complicate its diagnosis, and pituitary surgery can be performed inadvertently. The symptoms of ectopic acromegaly and the GH and IGF-1 levels seen are not always different from those encountered in classical acromegaly. Although GHRH measurement can greatly aid the differential diagnosis, it is not routinely assessed at diagnosis in acromegaly. Functional imaging techniques, such as somatostatin receptor scintigraphy, might reveal the presence of a NET, but again, these techniques would not be useful in the routine workup of the > 99% of patients with pituitary adenoma-related acromegaly.

Pituitary magnetic resonance imaging (MRI) has not been considered informative in ectopic acromegaly. Different imaging characteristics have been described, including pituitary enlargement, pituitary adenoma, empty sella, or even a normal gland (3). Moreover, even in cases of an enlarged pituitary, where pituitary hyperplasia is suspected, establishing the difference between pituitary hyperplasia and pituitary adenoma based on imaging is often difficult. The relative utilities of different MRI series in characterizing the pituitary in ectopic acromegaly, however, have not been adequately studied to date. In particular, the T2-weighted (T2W) pituitary MRI signal has not been assessed in ectopic acromegaly, whereas studies in pituitary acromegaly have revealed an important role of T2W signal in relation to clinical behavior (4-7). To address this, we performed a multicenter, retrospective study analyzing the imaging characteristics of pituitary tissue in ectopic acromegaly at diagnosis and during follow-up, with a special focus on the T2W signal.

Methods

We performed a Medline search of the English literature using the terms “ectopic,” “acromegaly,” and “GHRH” to identify publications dealing with ectopic acromegaly since the advent of MRI in 1992. Because previous studies did not systematically report T2W series (only gadolinium-enhanced T1-weighted series were typically reported), we contacted authors of publications to obtain additional T2W sequences, if available. Additionally, an international case-finding process was performed at tertiary referral centers to identify previously unpublished cases of acromegaly secondary to pathologically proven ectopic GHRH secretion. Only cases in which T2W series were available were included in the analysis. For these patients, demographic, clinical, biochemical, and histological data were gathered, as well as information regarding treatment of the acromegaly and of the underlying NET and the responses to treatment. Diagnostic pituitary MRI examinations, as well as follow-up MRI scans, whenever available, were analyzed.

Diagnosis of acromegaly was established in each medical center based on generally used criteria: an IGF-1 level above the normal values for age and sex at the local laboratory and, in most cases, nonsuppressible GH values during an oral glucose tolerance test. Whenever available, GHRH values were reported. GHRH measurements were performed primarily at the laboratories of 2 coauthors at centers in Lyon, France (V.R.) and Munich, Germany (M.B.). These 2 groups regularly exchange samples to maintain consistency between the methods used. In Lyon, the assay used was described in Girard et al (8). In that assay plasma, GHRH was measured using an in-house double-antibody radioimmunoassay. The intra-assay coefficient of variation (CV) is < 6% and interassay CV is < 15%. In normal controls, the circulating GHRH concentration was below the detection limit of the assay (<60 ng/L). In Munich, GHRH plasma concentrations were measured by fluorescence immunoassay as described in Schopohl et al (9). Sensitivity was 100 pg/mL, intra-assay CV was < 11%, and interassay CV was < 15%. GHRH

values for the patients included in our study were above the cutoff of the assay (generally 60-100 ng/L), whereas in pituitary acromegaly, GHRH values are expected to be suppressed.

Pituitary T2W signal intensity was visually assessed and compared with that of the normal pituitary tissue if the latter was visible, or if not visible, to that of the gray matter of the temporal lobe, as we have previously described (4). If no focal lesion was seen, pituitary hyperplasia was defined by a pituitary height (measured on the midline in the coronal plane) that was above the upper limit of normal for the corresponding age and sex group based on the literature data (10,11). For cases in which the pituitary height was above the upper limit of the normal provided by one of the reference datasets, but within normal values for the other, we considered pituitary height to be borderline.

The study was performed under the approval of the Ethics Committee of the Centre Hospitalier de Liège covering anonymous data collection regarding the study participants.

All the patient information was encoded as anonymous data. Statistical analyses were performed using the R statistical package (12). Data were plotted and assessed for normal distribution. Because none of the variables showed a normal distribution, population spread was described using median and interquartile ranges (25th and 75th percentiles). Count variables were tested with the χ^2 test. Continuous variables were compared using the Mann-Whitney and Kruskal-Wallis tests.

Results

Patient Characteristics

We included 17 cases previously reported in the literature that had been investigated with T2W series either at diagnosis (14 cases) or during follow-up (3 cases). The international case-finding approach identified a further 13 unpublished cases, bringing the total to 30 cases of ectopic acromegaly with an MRI examination that included T2W series (Table 1). There were 22

females and 8 males. The median overall age at diagnosis of acromegaly was 42 years (Q1: 35; Q3: 55); the median age of diagnosis was younger in males (34.5 years) than females (50.5 years) ($P = 0.03$).

Acromegaly was diagnosed before the NET in 14 patients. In the remaining 16 patients that were first diagnosed with the NET, up to 30 years passed before the diagnosis of acromegaly. The underlying GHRH-secreting NET was a bronchial carcinoid in 17 patients, a pancreatic tumor in 10, an appendicular carcinoma in 1, a pheochromocytoma in 1, and a paraganglioma in another. In 10 cases, metastases were already present at the time of diagnosis.

Median IGF-1 levels at diagnosis were 2.8 × upper limit of normal (Q1: 2.5; Q3: 3.6). Median random GH levels were 16 µg/L. GHRH was assessed in 24 patients, with values ranging from 82 to > 17 000 ng/L. We found no relationship between GHRH values and IGF-1 levels, nor between GHRH values and the presence of a metastatic tumor. Four patients had previously diagnosed *MEN* mutations, but *MEN1* gene sequencing was not performed as part of this study. Twenty-three patients had surgery of the NET, with disease remission in 17 cases. Pituitary surgery was performed in 3 patients. First-generation somatostatin receptor ligands (SRLs) were administered in 16 patients (either when ectopic secretion of GHRH was not controlled after NET surgery, in patients for whom NET surgery was not performed, and in individual cases, before NET surgery).

MRI Features

Pretreatment

Initial pituitary MRI reports of the 17 previously published cases described pituitary hyperplasia in 9 cases, a normal pituitary in 4, a pituitary adenoma in 2 cases, pituitary apoplexy in the context of a pituitary adenoma and adjacent hyperplasia in 1 patient, and a partially empty sella in 1 case. By comparing the pituitary dimensions with published reference values, we

classified 14 of the cases as being consistent with hyperplasia, 1 had an adenoma, 1 had a partially empty sella, and another had a borderline pituitary height. Including histological results suggestive of pituitary hyperplasia in the patient with pituitary apoplexy, the number of cases of hyperplasia rose to 15/17. After evaluation of their T2W signal, in all but 2 of the 17 cases the pituitary was T2-hypointense. The remaining patients correspond to the 1 with borderline pituitary height who had a T2-isointense pituitary and the patient with pituitary apoplexy with a T2-hyperintense, heterogeneous pituitary. Three of the T2-hypointense pituitaries were heterogeneous, exhibiting small T2W hyperintense regions.

For the 13 unpublished cases, 9 had pituitary hyperplasia (median pituitary height of 13 mm), 1 had borderline pituitary height (6 mm), 2 had normal pituitary glands (4 mm), and 1 had a partially empty sella (2 mm). The T2W signal was hypointense in 10 cases, isointense in 2, and hyperintense in 1 case. The T2W signal was heterogeneous for the T2-hyperintense pituitary and for 1 T2-hypointense case. The T2W signal was hypointense in 8/9 cases of hyperplasia, in the case of borderline pituitary height and in the patient with a partially empty sella. The 2 T2W-isointense cases corresponded to the patients with normal pituitary volumes. For the case with T2-hyperintense hyperplasia, the most likely diagnosis was metastasis because this patient also had multiple brain metastases.

Overall, among the total of 30 cases, pituitary hyperplasia was found in 24 cases with borderline increased tumor size in a further 2 cases. In the remaining 4 cases, the pituitary gland height was not increased for the patient's age (either normal-sized pituitaries in 2 patients or partially empty sella in 2 other patients). The median pituitary height was 9.5 mm. Pituitary height was never more than 18 mm except for 1 case with associated metastasis and 1 case with pituitary apoplexy. There was a weak negative correlation (r = -0.37, P = 0.04) between pituitary height and age at diagnosis with the oldest patient in the series, aged 84 years, having a partially empty sella.

T2-weighted signal was hypointense in 25/30 cases, isointense in 3, and hyperintense in 2 cases. In 4 cases with T2-hypointense pituitaries, small T2 hyperintense spots, probably of necrotic or hemorrhagic origin, were observed.

Normal pituitary gland tissue was never visualized, which differs from the situation of acromegaly resulting from a pituitary adenoma in which normal pituitary tissue is usually compressed on 1 side of the sella (Fig. 1). Invasion of the cavernous or sphenoid sinus was not found in any of the cases. There were no detectable changes of the sellar floor, and the pituitary stalk did not appear deviated. In the few cases in which dynamic imaging with gadolinium injection was performed, delayed pituitary enhancement was shown.

In 27/30 cases, the pituitary MRI was not consistent with a pituitary adenoma. One case had a probable pituitary metastasis, which most likely developed in a hyperplastic pituitary, 1 other patient with multiple endocrine neoplasia type 1 (MEN1) had a collision lesion (a small pituitary adenoma in the setting of a hyperplasic, T2-hypointense pituitary), and 1 patient had a pituitary apoplexy.

Posttreatment

In 21/30 patients, MRI examinations including T2W sequences were also performed either after surgery of the NET, after pituitary surgery, and/or after treatment with SRLs. The duration of SRL therapy varied from 3 months to 11 years. Among the patients treated with NET surgery, a follow-up MRI scan was available in 15/23 cases. Pituitary hyperplasia shrank in 13 cases, whereas 1 had a stable volume and another had an increase in pituitary volume. In this latter case, pituitary volume increased because of the enlargement of the associated collision pituitary adenoma in a MEN1 patient. Pituitary T2W signal remained hypointense, although the hypointensity was less pronounced than at diagnosis in 11 cases and changed from hypointense to isointense in 4. In these last 4 cases, the patients were considered cured, and all biological

values normalized. However, in 4 other cases in which remission was obtained, the T2W did not change appreciably in hypointensity vs the diagnostic MRI.

Among the 8 patients with follow-up MRIs who received SRL treatment and were not cured with NET surgery or in whom NET surgery was not performed, pituitary shrinkage was found in 6 patients. One patient had a stable pituitary volume. Increased tumor volume was found in 1 patient suspected of having both pituitary metastasis and hyperplasia, with a T2-hyperintense pituitary mass corresponding to the pituitary metastasis. The 6-month follow-up MRI scan of this last patient revealed pituitary tumor volume increase despite maximal medical treatment. The diagnosis of pituitary metastasis was supported by the appearance of multiple brain metastases. Except for that patient, the T2-weighted signal on follow-up MRI scan in SRL-treated patients was hypointense, and in only 1 case was the hypointensity less pronounced than at diagnosis.

Discussion

Ectopic GHRH secretion is an exceptionally rare cause of acromegaly that is responsible for < 1% of cases of acromegaly, which is itself an already rare disease. This is the first study to thoroughly analyze the pituitary MRI features, including T2-weighted sequences, in a large series of 30 patients diagnosed with ectopic acromegaly resulting from GHRH hypersecretion. We confirm that the pituitary in patients with ectopic GHRH secretion is usually hyperplastic. In the majority of cases, even in patients with normal or partially empty sella, the pituitary is T2-hypointense.

Acromegaly secondary to GHRH hypersecretion from a NET has similar clinical and biological characteristics to those of acromegaly resulting from GH-secreting pituitary adenomas. Patients diagnosed with ectopic acromegaly are only slightly younger (36-41 years) than patients with pituitary acromegaly (45 years) (3,13,25). Females are more frequent among ectopic

acromegaly patients; in the largest series published, more than 2/3 patients were females, which mirrors our findings (3,13). The delay between first acromegaly symptoms and diagnosis of acromegaly is similar in ectopic and pituitary acromegaly, at around 8 years. IGF-1 values at diagnosis are also similar in pituitary and ectopic forms of acromegaly, with median values around 2.6- to 2.7-fold the upper limit of normal, which was also seen in the current series. As is the case with somatotropinomas being larger in younger patients (25), in ectopic acromegaly, there also seems to be a correlation, albeit weak in our series, between age at diagnosis and pituitary height, with younger patients developing greater hyperplasia.

Differentiating between pituitary hyperplasia and adenoma is an important step in the assessment of acromegaly and in identifying the origin of the hormonal disturbance as pituitary GH hypersecretion or ectopic, extrapituitary GHRH overproduction. It is generally considered that pituitary MRI does not provide enough evidence for a definitive diagnosis of ectopic acromegaly. In a series of 20 patients with ectopic acromegaly and available pituitary imaging, Garby et al found 8 cases of hyperplasia, 5 pituitary adenomas, 5 cases with a normal pituitary, and 2 with a microcystic lesion (13). A series of 98 cases of ectopic acromegaly from the English language literature published between 1974 and 2011, many of which were only explored by computed tomography, found 41 cases with an enlarged pituitary, 27 cases of adenoma, 2 with empty sella, 18 normal pituitaries, and 2 microcystic lesions (3). Of the 98 cases, 30 were operated on for presumed somatotropinomas. Correct identification of the source of acromegaly (pituitary or ectopic) is then of major importance to avoid unnecessary pituitary surgery.

The threshold between hyperplasia and normal pituitary height is not clearly defined in general endocrine practice. The normal pituitary height by age and sex has been reported in large series of individuals (10,11). We used these reference values to classify the 30 cases included in this study to avoid false-negative visual assessments. For instance, a pituitary height of 7 mm may

seem unremarkable in a 66-year-old man, but the mean height at this age and sex is nearly 2 mm less according to 1 reference series, thereby suggesting hyperplasia. Differential diagnosis between pituitary hyperplasia and pituitary adenoma can be subtle. In our series, hyperplasia was symmetrical with a pituitary height less than 20 mm and a sellar floor that was unchanged or had minor symmetrical changes. Clinical symptoms of optic chiasm compression are not to be expected with moderate hyperplasia that usually does not reach the optic chiasm. In our series, there was no invasion of the cavernous or the sphenoid sinuses. An important point is that, unlike what is generally found in patients with pituitary adenomas, normal pituitary tissue was not identified (Fig. 1). Applying these criteria, no MRI pattern similar to a pituitary adenoma was found in our series of 30 patients, apart from 1 patient with a very likely metastasis that masked the pituitary hyperplasia, from 1 MEN1 patient with a collision lesion and from a patient with pituitary apoplexy, having a somatotropinoma and hyperplasia on histological analysis. Regarding this latter patient, he had already had a cerebral MRI scan for an unrelated reason 20 months before the diagnosis of apoplexy and at the time, the pituitary was already slightly hyperplastic and T2-hypointense. This indicates that chronic stimulation of the somatotrope cells by GHRH can induce adenoma formation, as already described as occurring via a different molecular mechanism in a genetic context (26). However, this phenomenon is most likely rare and potentially only induced by marked GHRH hypersecretion because we have not identified other similar cases of adenomas detectable by MRI scan in our series. Of course, very small adenomatous changes cannot be excluded without histological analyses.

In recent years, several studies have shown an important role for T2-weighted MRI sequences in the assessment of acromegaly (4,6,27,28). T2-weighted adenoma signal permits discrimination between different types of somatotropinomas in terms of the magnitude of GH secretion, adenoma characteristics (size, local extension, invasiveness), response to SRL and,

most likely, histological features (5,7). However, T2-weighted series of pituitary MRIs have never been previously analyzed in the diagnosis of GHRH-related acromegaly. In our series, 25/30 patients had T2-hypointense pituitaries and, among them, 22 pituitaries were hyperplastic. Only 2 patients had T2-hyperintense pituitaries, and these patients suffered from either the extremely rare occurrence of associated pituitary metastasis or pituitary apoplexy. Three patients had T2-isointense pituitaries and were patients with normal or only slightly enlarged pituitaries. The explanation for why densely granulated adenomas as well as pituitary hyperplasia from GHRH hypersecretion appears T2 hypointense is still unknown. According to Hagiwara et al (27), the amounts of amyloid, fibrous tissue, and iron contained in somatotropinomas seem to have little influence on signal intensity. Densely granulated adenomas have numerous secretory granules, whereas other pituitary adenomas have few or no secretory granules. It could be that protein-rich secretory granules influence signal intensity on T2-weighted images. T2-weighted pituitary hypointensity returns to isointensity in a few cases after successful NET surgery along with pituitary shrinkage (Fig. 2). However, for unknown reasons, T2-weighted pituitary signal remains hypointense in other patients for as long as 10 years of follow-up despite complete normalization of all biological parameters and remission of the NET (Fig. 3). This persistence of the T2-hypointense signal argues in favor of GHRH-driven alterations in the ultrastructure of the pituitary somatotrope cells that are partially irreversible.

Although surgical excision of the GHRH-secreting NET along with resection of metastases is the ideal treatment, SRLs have also shown some efficacy both in terms of tumor volume reduction and on biochemical responses in terms of GHRH, GH, and IGF-1 lowering (29). In our series, most patients on SRLs were found to exhibit pituitary shrinkage, whereas T2 hypointensity most often remained similar in magnitude to that seen at diagnosis. Overall, it

seems that a relationship exists between the change of T2 hypointensity and the biological response to treatment of the GHRH-induced pituitary hyperplasia.

Limitations of the study include the lack of complete availability of retrospective quantitative measurement of T2W signal. However, we have previously demonstrated that a visual approach through comparison of pituitary vs gray matter T2-weighted signal represents a valid evaluation (4).

Conclusions

This large series identified demographic, tumoral, and radiological factors that can assist in the diagnosis of ectopic acromegaly (Fig. 4). Demographically, most patients are female (>70%), and males present at a younger age. In 50% of cases, the diagnosis of acromegaly precedes that of the NET. Ninety percent of NETs causing ectopic acromegaly are of bronchial or pancreatic origin. The typical pituitary MRI appearance of ectopic acromegaly is a slightly to moderately enlarged, T2-hypointense gland, without cavernous sinus invasion or optic chiasm compression. In ectopic acromegaly, normal pituitary tissue is not visualized on MRI scans. Most pituitaries (80%) have a hyperplastic appearance, and pituitary height rarely exceeds 18 mm. In the infrequent cases in which ectopic acromegaly patients have a normal-sized pituitary or a partially empty sella, a hypointense T2-weighted signal is an important clue that ought to raise suspicion of a potential ectopic GHRH source. Pituitary MRI with T2-weighted sequences may therefore be more helpful than previously thought in differentiating between pituitary and ectopic acromegaly.

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Disclosures

The authors have nothing to disclose.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided

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Table 1.Characteristics of patients with ectopic acromegaly included in the series

Patient no. (reference)	Sex	Age at diagnosis, y	First diagnosed (NET or acromegaly)	NET site	GH (µg/L)	IGF-1 ULN	GHRH (ng/L)	Pituitary height on first MRI (mm)	Pituitary T2W signal at diagnosis	NET surgery	SRL	Pituitary surgery
1[a] (13)	F	36	NET	Pancreas MTS	60	4.2	1614	14	Hypo	NO	YES	NO
2[a] (13)	M	67	Acro	Pancreas MTS	3	1.1	545	6	Hypo	NO	YES	NO
3[a] (13)	F	34	NET	Pancreas MTS	2.5	2.2	1297	7	Hypo	YES	YES	NO
4[a] (13)	F	34	Acro	Pancreas MTS	43	3.4	512	18	Hypo heterogeneous	YES	NO	YES
5[a] (14)	M	36	NET	Bronchial MTS	49.8	2.6	4654	7	Hypo	YES	YES	NO
6[a] (15)	F	39	Acro	Bronchial	16	2.1	NA	8	Hypo	YES	NO	NO
7[a] (16)	F	59	Acro	Bronchial	25	2.7	17727	17	Hypo heterogeneous	YES	YES	NO
8[a] (17)	F	60	Acro	Pancreatic	57	1.3	604	2	Hypo	YES	NO	NO
9[a] (18)	F	57	NET	Pancreatic	13.5	3.9	1273	11	Hypo	YES	NO	NO
10[a] (13)	F	28	Acro	Bronchial	26	4.3	1173	10	Hypo	YES	YES	YES
11[a] (19)	F	51	Acro	Appendix	6	2.8	4560	8	Hypo	YES	NO	NO
12[a] (20)	F	42	Acro	Bronchial	NA	4.2	82	10	Hypo	YES	YES	NO
13[a] (21)	F	56	Acro	Bronchial	6.1	3.5	100	6	Iso	YES	NO	NO
14[a] (13)	F	77	NET	Bronchial	27.6	2.9	7528	12	Hypo	NO	YES	NO
15[a] (22)	F	43	Acro	Bronchial	44	3.3	NA	12	Hypo	YES	YES	NO
16[a] (23)	M	22	NET	Bronchial MTS	2	2.8	NA	25	Hyper heterogeneous	NO	YES	YES
17[a] (24)	M	18	NET	Pancreatic	39	2	327	8	Hypo heterogeneous	YES	NO	NO
18	M	32	NET	Pheochromocytoma	NA	2.7	NA	6	Hypo	YES	NO	NO
19	F	53	NET	Bronchial MTS	9	3.4	8316	13	Hypo	NO	YES	NO
20	F	39	NET	Bronchial MTS	32	2.5	170	23	Hyper heterogeneous	NO	YES	NO
21	F	84	NET	Pancreatic	3.25	NA	141	2	Hypo	NO	YES	NO
22	F	53	NET	Pancreatic	4.5	2.8	542	4	Iso	YES	NO	NO
23	F	53	Acro	Bronchial	13	NA	250	4	Iso	YES	NO	NO
24	F	50	NET	Pancreatic	7.3	2	398	8	Hypo heterogeneous	YES	NO	NO
25	M	42	NET	Bronchial	NA	NA	3000	9	Hypo	YES	YES	NO
26	F	35	Acro	Bronchial	27.9	3.7	NA	13	Hypo	YES	NO	NO
27	M	36	Acro	Bronchial	7.4	2.6	1312	11	Hypo	YES	NO	NO

Table 1.Characteristics of patients with ectopic acromegaly included in the series

Patient no. (reference)	Sex	Age at diagnosis, y	First diagnosed (NET or acromegaly)	NET site	GH (µg/L)	IGF-1 ULN	GHRH (ng/L)	Pituitary height on first MRI (mm)	Pituitary T2W signal at diagnosis	NET surgery	SRL	Pituitary surgery
28	F	36	Acro	Bronchial	14	4	NA	17	Hypo	YES	YES	NO
29	M	33	NET	Bronchial MTS	34	5.2	1440	9	Hypo	YES	NO	NO
30	F	58	NET	Paraganglioma MTS	23.8	3.3	164	13	Hypo	NO	YES	NO

Abbreviations: Acro, acromegaly; MRI, magnetic resonance imaging; MTS, metastatic; NA, not applicable; NET, neuroendocrine tumor; SRL, somatostatin receptor ligand; T2W, T2-weighted; ULN, upper limit of normal.

[a]Previously reported in the literature.

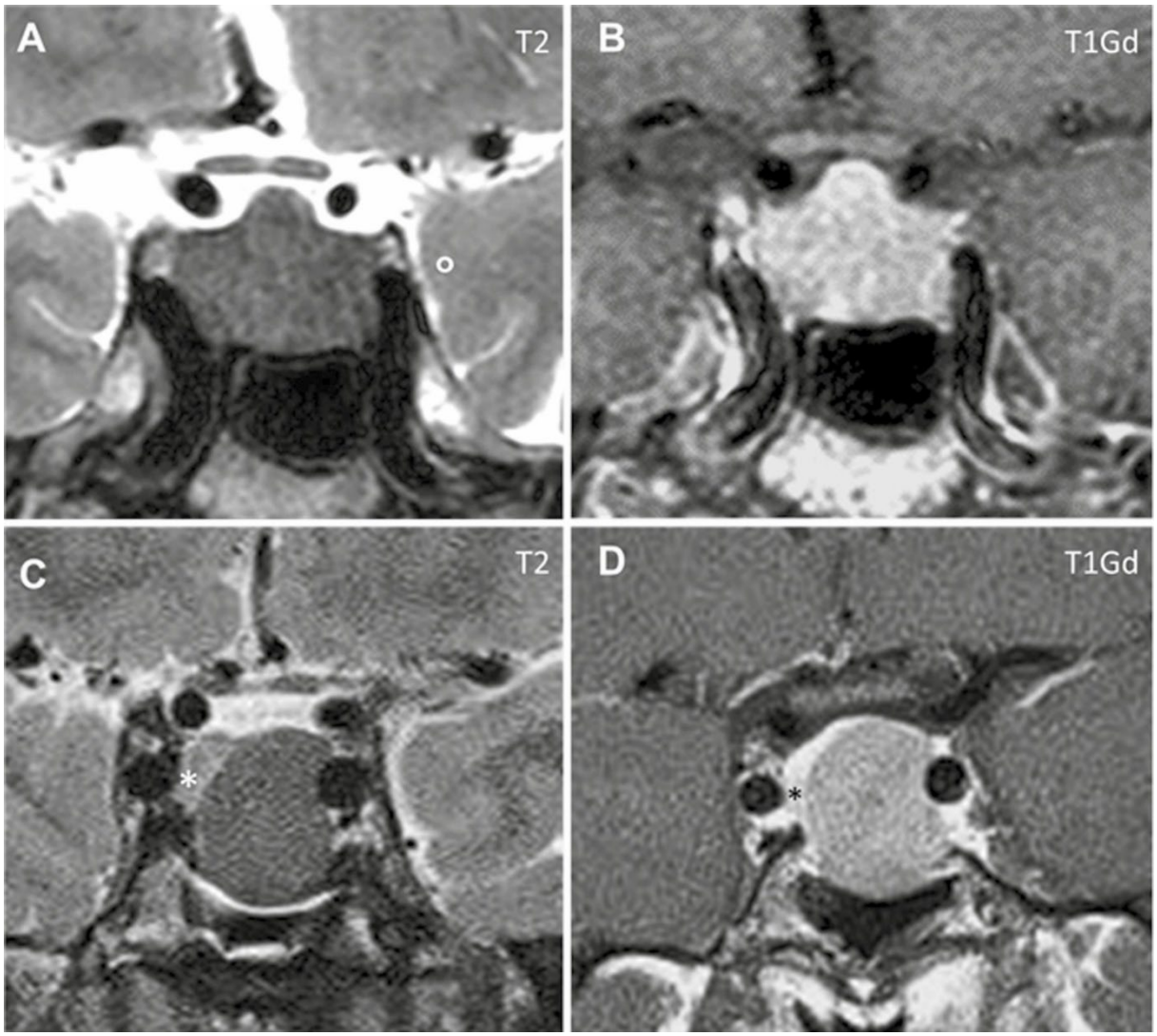

Figure 1. Differences between the MRI appearance of pituitary hyperplasia (A, B) and that of a T2-hypointense somatotropinoma (C, D). Symmetrical enlargement of the pituitary bearing a T2-hypointense signal intensity (when compared with that of the temporal cortex, marked with °) in a normally appearing sella turcica (A, B) vs the presence of a T2-hypointense tumor mass developed more toward the left side and toward the sphenoid sinus, deforming the sellar floor and leaving the normal pituitary tissue on the right side of the sella (marked with *). (A, C) T2-weighted coronal sections; (B, D) T1-weighted gadolinium-enhanced coronal sections.

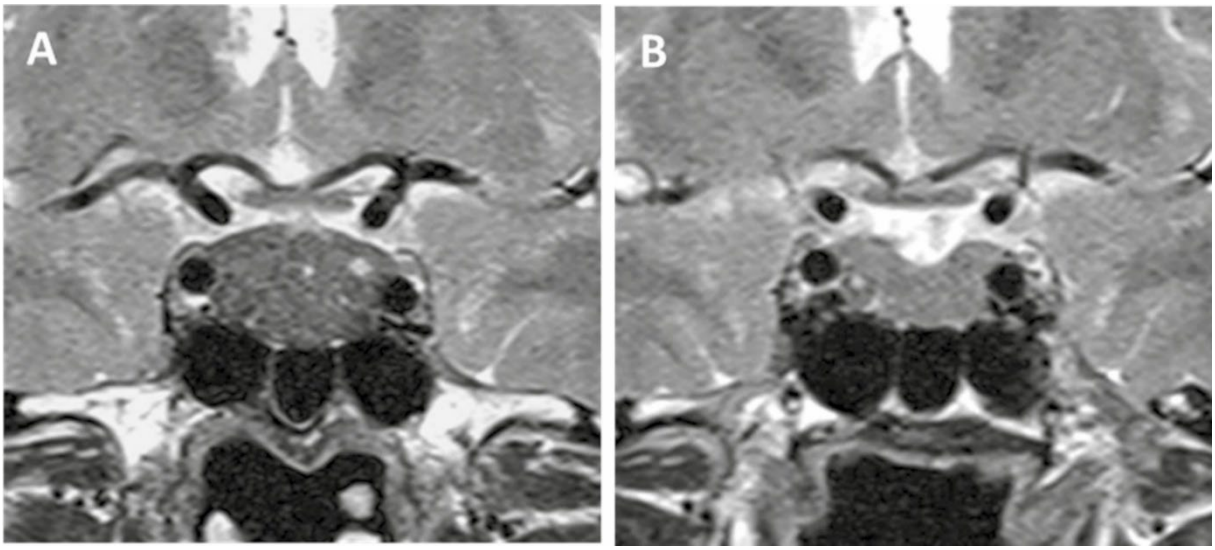

Figure 2. (A) Slightly heterogeneous, T2-hypointense pituitary hyperplasia with T2-hyperintense foci in a 59-year-old female patient diagnosed with acromegaly (IGF-1 2.7 × ULN) from a GHRH-producing bronchial tumor (GHRH levels at diagnosis 17 727 ng/L). (B) After thoracic surgery, normalization of IGF-1 and GHRH levels with shrinkage of the pituitary and a T2W signal that became isointense.

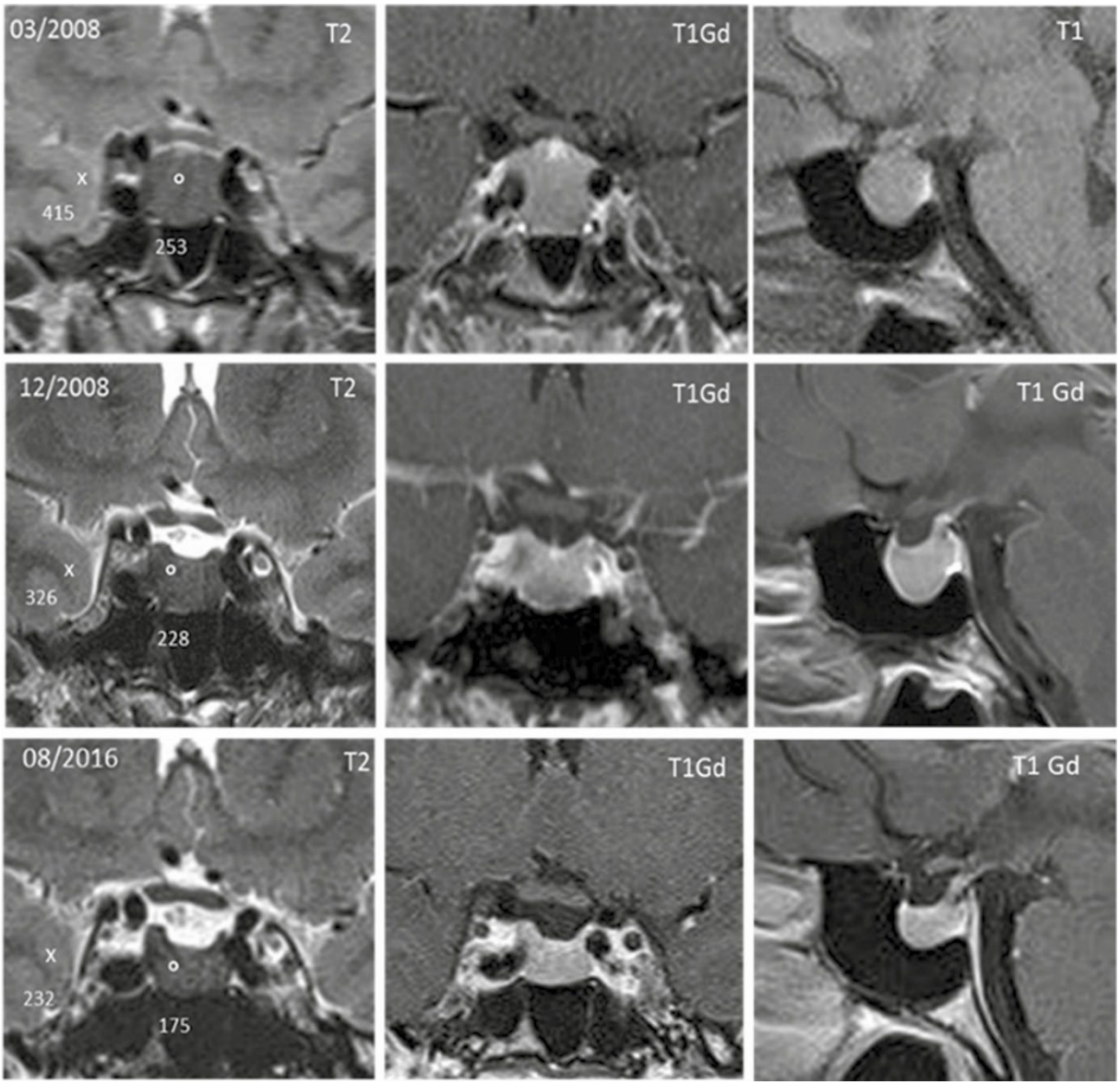

Figure 3. Evolution of the pituitary after treatment of a GHRH-producing bronchial carcinoma in a 35-year-old female patient diagnosed with acromegaly (IGF-1 3.7 × ULN). Rapid decrease in pituitary size after surgery of the bronchial carcinoma (performed in October 2008), which led to normalization of IGF-1, with further pituitary shrinkage in time. Despite biochemical cure, the pituitary T2-weighted signal intensity remained hypointense (region of interest values for the pituitary and the temporal gray matter are found on each T2-weighted section). Each line presents sections from MRI performed at the same time: the first column contains T2-weighted coronal sections, the second line contains gadolinium-enhanced coronal sections, and the third line contains gadolinium-enhanced sagittal sections.

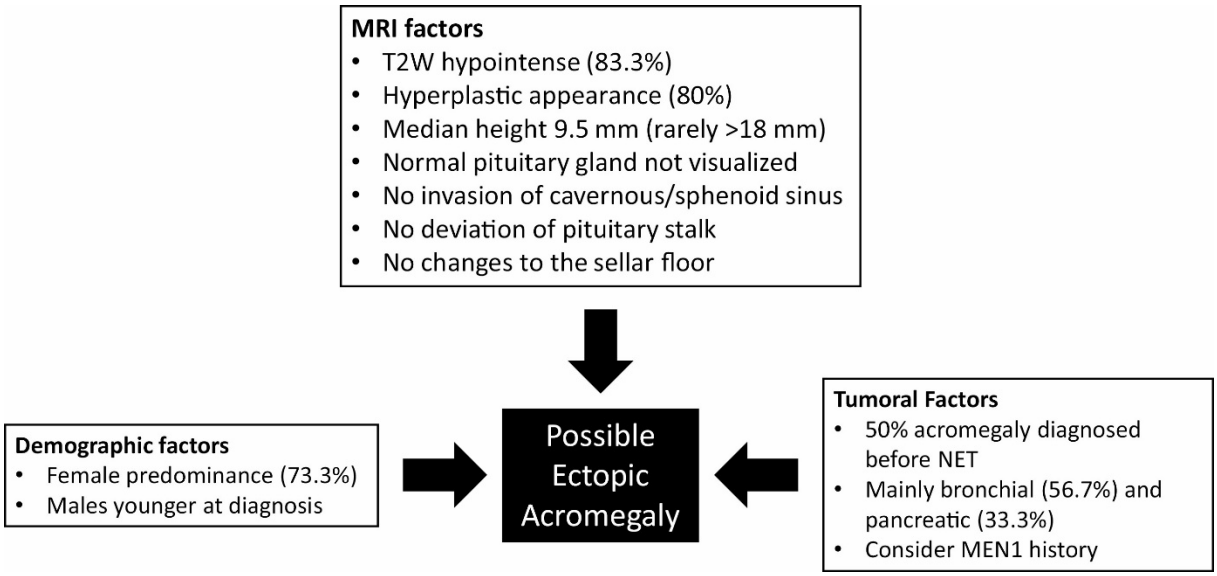

Figure 4. Summary of MRI, demographic, and tumoral factors that can assist when considering a potential diagnosis of ectopic acromegaly resulting from a neuroendocrine tumor.