Pituitary MRI Features in Acromegaly due to 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 Bildingmaier[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].

Departments of [1]Endocrinology and [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, Rotterdam, The Netherlands

[4] Department of Endocrinology, Hospital Italiano de Buenos Aires, 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, 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, United Kingdom

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

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

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

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

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

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

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

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

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

[16] Department of Endocrinology, Diabetes and Isotope Therapy, Wroclaw Medical University, Wroclaw, Poland

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

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

[19] Service d'Endocrinologie, Centre Hospitalier Universitaire de Grenoble, Grenoble, France

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

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

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

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

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

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

[26] Department of Endocrinology, The Centre of Postgraduate Medical Education, Warsaw, Poland

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

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

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

Disclosure summary: The authors have nothing to disclose.

Corresponding

Albert Beckers MD, PhD

albert.beckers@chuliege.be

ORCID ID 0000-0001-6351-1367

Jean-François Bonneville MD, PhD

bonnevillejf@gmail.com

ORCID ID 0000-0002-9562-4793

Abstract

Context: Ectopic acromegaly is a consequence of rare neuroendocrine tumors (NET) that secrete growth hormone releasing hormone (GHRH). This abnormal GHRH secretion drives growth hormone (GH) and insulin-like growth factor 1 (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 its rarity, the imaging characteristics of the pituitary in ectopic acromegaly have not been analyzed in depth in 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: 30 ectopic acromegaly patients due to 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 to 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

Introduction

Acromegaly is a rare endocrine disorder with an estimated prevalence of 10.5 cases per 100000 individuals [1]. It is usually due to growth hormone (GH) hypersecretion from a pituitary adenoma. Less than 1% of cases of acromegaly are secondary to ectopic secretion of growth hormone releasing hormone (GHRH), usually from a bronchial or pancreatic neuroendocrine tumor (NET), although other sources of abnormal GHRH secretion have been described (e.g. 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 insulin-like growth factor 1 (IGF-1) levels are not always different from those encountered in classical acromegaly. While 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 neuroendocrine tumor, but again, these techniques would not be useful in the routine work-up of the >99% of patients with pituitary adenoma-related acromegaly.

Pituitary magnetic resonance imaging (MRI) has not been considered as being 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 frequently 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 studied 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. As previous studies did not systematically report T2W series (only gadolinium enhanced T1W 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, 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 MRIs, whenever available, were analyzed.
Diagnosis of acromegaly was established in each medical center based on generally-employed criteria: an elevated IGF-1 level above the normal values for age and sex at the local laboratory and, in most cases, non-suppressible GH values during an oral glucose tolerance test (OGTT). Whenever available, GHRH values were reported. GHRH measurements were performed primarily at the laboratories of two coauthors at centers in Lyon, France (V.R.) and Munich, Germany (M.B.). These two groups regularly exchange samples to maintain consistency between the methods used. In Lyon, the assay used was described in Girard P et al [8]. In that assay plasma GHRH was measured using an in-house double-antibody RIA. The intra-assay CV is <6%, and inter-assay CV is <15%. In normal controls, the circulating GHRH concentration was below the detection limit of the assay (<60 ng/liter). In Munich, GHRH plasma concentrations were measured by fluorescence immunoassay (FIA) as described in Schopohl J et al [9]. Sensitivity was 100 pg/ml, intra-assay CV<11%, and inter-assay CV<15%. GHRH values for the patients included in our study were above the cut-off of the assay (generally 60 to 100 ng/l), whereas in pituitary acromegaly, GHRH values are expected to be suppressed.

Pituitary T2W signal intensity was visually assessed and compared to that of the normal pituitary tissue if the latter was visible, or if not visible, to that of the grey 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 literature data [10,11]. For cases where 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. Since none of the variables showed a normal distribution, population spread was described using median and interquartile ranges (25^{th} and 75^{th} percentiles). Count variables were tested with the Chi-square 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 eight 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 neuroendocrine tumor (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 one, a pheochromocytoma in one and a paraganglioma in another. In ten cases, metastases were already present at the time of diagnosis.

Median IGF-1 levels at diagnosis were 2.8 x ULN (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 *MEN1* 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 three 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

Pre-treatment

Initial pituitary MRI reports of the 17 previously published cases described pituitary hyperplasia in nine cases, a normal pituitary in four, a pituitary adenoma in two cases, pituitary apoplexy in the context of a pituitary adenoma and adjacent hyperplasia in one patient and a partially empty sella in one case. By comparing the pituitary dimensions with published reference values, we classified 14 of the cases as being consistent with hyperplasia, one had an adenoma, one 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 rises to 15/17. After evaluation of their T2W signal, in all but two of the 17 cases the pituitary was T2-hypointense. The remaining patients correspond to the one 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, nine patients had pituitary hyperplasia (median pituitary height of 13 mm), one had borderline pituitary height (6 mm), two had normal pituitary glands (4 mm) and one had a partially empty sella (2 mm). The T2W signal was hypointense in ten cases, isointense in two

and hyperintense in one case. The T2W signal was heterogeneous for the T2-hyperintense pituitary and also for one 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 two T2W-isointense cases corresponded to the patients with normal pituitary volumes. For the case with T2-hyperintense hyperplasia, the most likely diagnosis was metastasis, as 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 two cases. In the remaining four cases the pituitary gland height was not increased for the patient's age (either normal-sized pituitaries in two patients or partially empty sella in two other patients). The median pituitary height was 9.5 mm. Pituitary height was never more than 18 mm except for one case with associated metastasis and one 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, having a partially empty sella.

T2-weighted signal was hypointense in 25/30 cases, isointense in three and hyperintense in two cases. In four 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 due to a pituitary adenoma where normal pituitary tissue is usually compressed on one side of the sella (Figure 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 where dynamic imaging with gadolinium injection was performed, it showed delayed pituitary enhancement.

In 27/30 cases, the pituitary MRI was not consistent with a pituitary adenoma. One case had a probable pituitary metastasis, that most likely developed in a hyperplastic pituitary, one 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 one patient had a pituitary apoplexy.

Post-treatment

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 three months to 11 years. Among the patients treated with NET surgery, a follow-up MRI was available in 15/23 cases. Pituitary hyperplasia shrank in 13 cases, whereas one had a stable volume and another had an increase in pituitary volume. In this latter case, pituitary volume increased due to 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 four. In these last four cases, the patients were considered cured and all biological values normalized. However, in four other

cases in which remission was obtained, the T2W did not change appreciably in hypointensity versus the diagnostic MRI.

Among the eight 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 six patients. One patient had a stable pituitary volume. Increase of tumor volume was found in one patient suspected of having both pituitary metastasis and hyperplasia, with a T2-hyperintense pituitary mass corresponding to the pituitary metastasis. The six-month follow-up MRI 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 in SRL-treated patients was hypointense, and in only one 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 due to 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 due to GH-secreting pituitary adenomas. Patients diagnosed with ectopic acromegaly are only slightly younger (36-41 years) than patients with pituitary acromegaly (45 years) [3,13,14]. Female patients are more frequent among ectopic acromegaly patients; in the largest series published, over 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 eight years. IGF-1 values at diagnosis are also similar in pituitary and ectopic forms of acromegaly, with median values around 2.6-2.7-fold ULN, which was also seen in the current series. As is the case with somatotropinomas being larger in younger patients [14], 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, extra-pituitary 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 eight cases of

hyperplasia, five pituitary adenomas, five cases with a normal pituitary and two 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, two with empty sella, 18 normal pituitaries and two microcystic lesions [3]. Of the 98 cases, 30 patients 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 one 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 (Figure 1). Applying these criteria, no MRI pattern similar to a pituitary adenoma was found in our series of 30 patients, apart from one patient with a very likely metastasis that masked the pituitary hyperplasia, from one 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 for an unrelated reason 20 months prior to 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 in a genetic context[15]. However, this phenomenon is most likely rare and potentially only induced by marked GHRH hypersecretion, as we have not identified other similar cases of adenomas detectable by MRI 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 [4,6,16,17]. 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 two 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 these were patients with normal or only slightly enlarged pituitaries. The explanation for why densely granulated adenomas as well as pituitary hyperplasia due to GHRH hypersecretion appears T2 hypointense is still unknown. According to Hagiwara [16], 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 while 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 (Figure 2). However, for unknown reasons, T2-weighted pituitary signal remains hypointense in other patients for as long as ten years of follow-up despite complete normalization of all biological parameters and remission of the NET (Figure 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.

While 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 [18]. In our series, most patients on SRLs were found to exhibit pituitary shrinkage, while 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 versus 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 (see Figure 4). Demographically, most patients are female (>70%), while 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. Most pituitaries (80%) have a hyperplastic appearance, and pituitary height rarely exceeds 18 mm. In the infrequent cases where 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.

Acknowledgements

The authors wish to acknowledge the following for their assistance and collaboration: Delphine Drui, Jorge Rojo Alvaro, Nienke R Biermasz, Mark Gurnell, Brigitte Delemer, Andrea Giustina, Antoine Tabarin and Jacqueline Trouillas

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.

References

1. Daly, A. F. & Beckers, A. The Epidemiology of Pituitary Adenomas. *Endocrinology and Metabolism Clinics of North America* (2020). doi:10.1016/j.ecl.2020.04.002

2. Asa, S. L. *et al.* A case for hypothalamic acromegaly: A clinicopathological study of six patients with hypothalamic gangliocytomas producing growth hormone-releasing factor. *J. Clin. Endocrinol. Metab.* (1984). doi:10.1210/jcem-58-5-796

3. Ghazi, A. A. *et al.* Ectopic acromegaly due to growth hormone releasing hormone. *Endocrine* (2013). doi:10.1007/s12020-012-9790-0

4. Potorac, I. *et al.* Pituitary MRI characteristics in 297 acromegaly patients based on T2-weighted sequences. *Endocr. Relat. Cancer* (2015). doi:10.1530/ERC-14-0305

5. Potorac, I. *et al.* T2-weighted MRI signal predicts hormone and tumor responses to somatostatin analogs in acromegaly. *Endocr. Relat. Cancer* (2016). doi:10.1530/ERC-16-0356

6. Heck, A. *et al.* Intensity of pituitary adenoma on T2-weighted magnetic resonance imaging predicts the response to octreotide treatment in newly diagnosed acromegaly. *Clin. Endocrinol. (Oxf).* (2012). doi:10.1111/j.1365-2265.2011.04286.x

7. Heck, A., Emblem, K. E., Casar-Borota, O., Bollerslev, J. & Ringstad, G. Quantitative analyses of T2-weighted MRI as a potential marker for response to somatostatin analogs in newly diagnosed acromegaly. *Endocrine* (2016). doi:10.1007/s12020-015-0766-8

8. Girard, P. *et al.* Pharmacokinetics of human growth hormone releasing factor (hGRF-44 NH2) in normal men after intravenous administration of a large range of doses. *Eur. J. Clin. Pharmacol.* (1987). doi:10.1007/BF00637679

9. Schopohl, J. *et al.* Plasma growth hormone (GH)- releasing hormone levels in patients with lung carcinoma. *Clin. Endocrinol. (Oxf).* (1991). doi:10.1111/j.1365-2265.1991.tb00326.x

10. Tsunoda, A., Okuda, O. & Sato, K. MR height of the pituitary gland as a function of age and sex: Especially physiological hypertrophy in adolescence and in climacterium. *Am. J. Neuroradiol.* (1997).

11. Yadav, P., Singhal, S., Chauhan, S. & Harit, S. MRI evaluation of size and shape of normal pituitary gland: Age and sex related changes. *J. Clin. Diagnostic Res.* (2017). doi:10.7860/JCDR/2017/31034.10933

12. R Core Team. R Core Team (2014). R: A language and environment for statistical computing.

R Found. Stat. Comput. Vienna, Austria. URL http//www.R-project.org/. (2014).

13. Garby, L. *et al.* Clinical characteristics and outcome of acromegaly induced by ectopic secretion of Growth Hormone-Releasing Hormone (GHRH): A French nationwide series of 21 cases. *J. Clin. Endocrinol. Metab.* (2012). doi:10.1210/jc.2011-2930

14. Petrossians, P. *et al.* Acromegaly at diagnosis in 3173 patients from the Liège Acromegaly Survey (LAS) Database. *Endocr. Relat. Cancer* (2017). doi:10.1530/ERC-17-0253

15. Villa, C. *et al.* Hyperplasia-adenoma sequence in pituitary tumorigenesis related to aryl hydrocarbon receptor interacting protein gene mutation. *Endocr. Relat. Cancer* (2011). doi:10.1530/ERC-11-0059

16. Hagiwara, A. *et al.* Comparison of growth hormone-producing and non-growth hormone-producing pituitary adenomas: Imaging characteristics and pathologic correlation. *Radiology* (2003). doi:10.1148/radiol.2282020695

17. Puig-Domingo, M. *et al.* Magnetic resonance imaging as a predictor of response to somatostatin analogs in acromegaly after surgical failure. *J. Clin. Endocrinol. Metab.* (2010). doi:10.1210/jc.2010-0573

18. Boix, E., Picó, A., Pinedo, R., Aranda, I. & Kovacs, K. Ectopic growth hormone-releasing hormone secretion by thymic carcinoid tumour. *Clin. Endocrinol. (Oxf).* (2002). doi:10.1046/j.1365-2265.2002.01535.x

19. Fainstein Day, P. *et al.* Ectopic growth hormone-releasing hormone secretion by a metastatic bronchial carcinoid tumor: A case with a non hypophysial intracranial tumor that shrank during long acting octreotide treatment. *Pituitary* (2007). doi:10.1007/s11102-007-0019-9

20. Álvaro, J. R. *et al.* Ectopic acromegaly due to a bronchial carcinoid. *An. Sist. Sanit. Navar.* (2013). doi:10.4321/s1137-66272013000300022

21. Kałużny, M. *et al.* Acromegaly due to ectopic growth hormone-releasing hormone secretion by lung carcinoid. *Polish Arch. Intern. Med.* (2020). doi:10.20452/pamw.15337

22. Mnif Feki, M. *et al.* Ectopic secretion of GHRH by a pancreatic neuroendocrine tumor associated with an empty sella. *Ann. Endocrinol. (Paris).* (2011). doi:10.1016/j.ando.2011.06.002

23. Zornitzki, T. *et al.* pNET co-secreting GHRH and calcitonin: ex vivo hormonal studies in human pituitary cells. *Endocrinol. Diabetes Metab. Case Reports* (2016). doi:10.1530/edm-15-0134

24. Chanson, P. Acromégalie. *Presse Medicale* (2009). doi:10.1016/j.lpm.2008.09.016

25. Gudbjartsson, T., Agnarsson, B. A., Palsson, P. S. & Johannesson, A. Acromegaly caused by ectopic growth hormone-releasing hormone production from a bronchial carcinoid tumor. *Thorac. Cardiovasc. Surg.* (2011). doi:10.1055/s-0030-1250341

26. Van Hoek, M. *et al.* Effects of somatostatin analogs on a growth hormone-releasing hormone secreting bronchial carcinoid, in vivo and in vitro studies. *J. Clin. Endocrinol. Metab.* (2009). doi:10.1210/jc.2008-1712

27. Stelmachowska- Banaś, M. *et al.* Ectopic acromegaly due to growth hormone–releasing hormone secretion from bronchial carcinoid causing somatotroph hyperplasia and partial pituitary insufficiency. *Polish Archives of Internal Medicine* (2019). doi:10.20452/pamw.4413

28. Lamback, E. B. *et al.* Growth hormone-releasing hormone-secreting pulmonary neuroendocrine tumor associated with pituitary hyperplasia and somatotropinoma. *Archives of endocrinology and metabolism* (2021). doi:10.20945/2359-3997000000395

29. Srirangam Nadhamuni, V. *et al.* GHRH secretion from a pancreatic neuroendocrine tumor causing gigantism in a patient with MEN1. *Endocrinol. Diabetes Metab. Case Reports* (2021). doi:10.1530/edm-20-0208

Table 1. Patient characteristics of patients with ectopic acromegaly included in the series. Cases marked with an * have previously been reported in the literature. NET – neuroendocrine tumor, SRL – somatostatin receptor ligands, MTS – metastatic.

Patient number (Reference)	Gender	Age at diagnosis	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*[13]	F	36	NET	PANCREAS MTS	60	4.2	1614	14	HYPO	NO	YES	NO
2*[13]	M	67	ACRO	PANCREAS MTS	3	1.1	545	6	HYPO	NO	YES	NO
3*[13]	F	34	NET	PANCREAS MTS	2.5	2.2	1297	7	HYPO	YES	YES	NO
4*[13]	F	34	ACRO	PANCREAS MTS	43	3.4	512	18	HYPO HETEROGENEOUS	YES	NO	YES
5*[19]	M	36	NET	BRONCHIAL MTS	49.8	2.6	4654	7	HYPO	YES	YES	NO
6*[20]	F	39	ACRO	BRONCHIAL	16	2.1	NA	8	HYPO	YES	NO	NO
7*[21]	F	59	ACRO	BRONCHIAL	25	2.7	17727	17	HYPO HETEROGENEOUS	YES	YES	NO
8*[22]	F	60	ACRO	PANCREATIC	57	1.3	604	2	HYPO	YES	NO	NO
9*[23]	F	57	NET	PANCREATIC	13.5	3.9	1273	11	HYPO	YES	NO	NO
10*[13]	F	28	ACRO	BRONCHIAL	26	4.3	1173	10	HYPO	YES	YES	YES
11*[24]	F	51	ACRO	APPENDIX	6	2.8	4560	8	HYPO	YES	NO	NO
12*[25]	F	42	ACRO	BRONCHIAL	NA	4.2	82	10	HYPO	YES	YES	NO
13*[26]	F	56	ACRO	BRONCHIAL	6.1	3.5	100	6	ISO	YES	NO	NO
14*[13]	F	77	NET	BRONCHIAL	27.6	2.9	7528	12	HYPO	NO	YES	NO
15*[27]	F	43	ACRO	BRONCHIAL	44	3.3	NA	12	HYPO	YES	YE	NO

											S	
16*[28]	M	22	NET	BRONCHIAL MTS	2	2.8	NA	25	HYPER HETEROGENEOUS	NO	YES	YES
17*[29]	M	18	NET	PANCREATIC	39	2	327	8	HYPO HETEROGENEOUS	YES	NO	NO
18	M	32	NET	PHEOCHROMO-CYTOMA	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
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

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 to that of the temporal cortex, marked with a °) in a normally-appearing sella turcica (A, B) versus the presence of a T2-hypointense tumor mass developed more towards the left side and towards the sphenoid sinus, deforming the sellar floor and leaving the normal pituitary tissue on the right side of the sella (marked with an *). (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 x ULN) due to a GHRH-producing bronchial tumor (GHRH levels at diagnosis 17727 ng/l). B. After thoracic surgery, normalization of IGF-1 and GHRH levels with shrinkage of the pituitary and a T2W signal that has become 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 x ULN). Rapid decrease in pituitary size after surgery of the bronchial carcinoma (performed in 10/2008) 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 gadolinium-enhanced coronal sections and the third line gadolinium-enhanced sagittal sections.

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

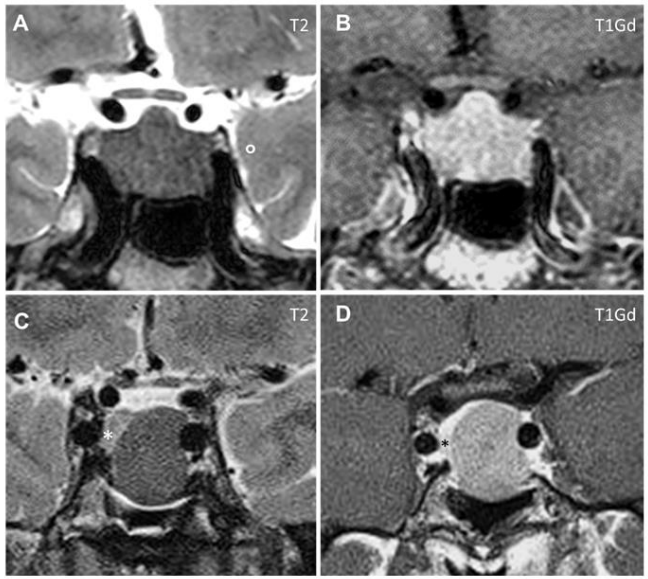

Figure 1

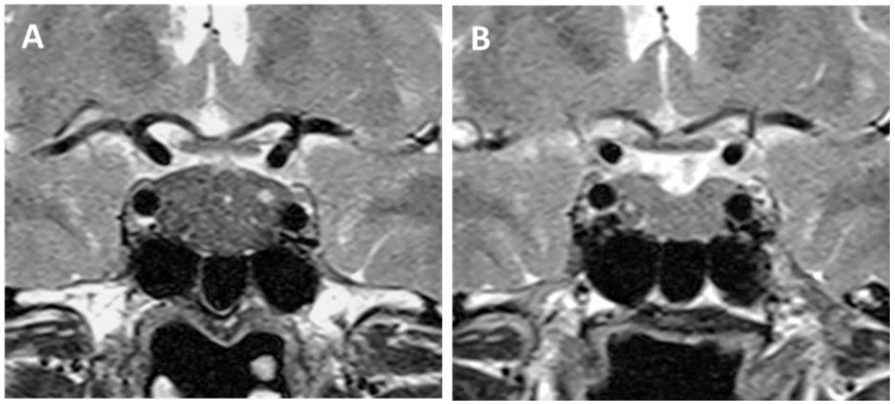

Figure 2

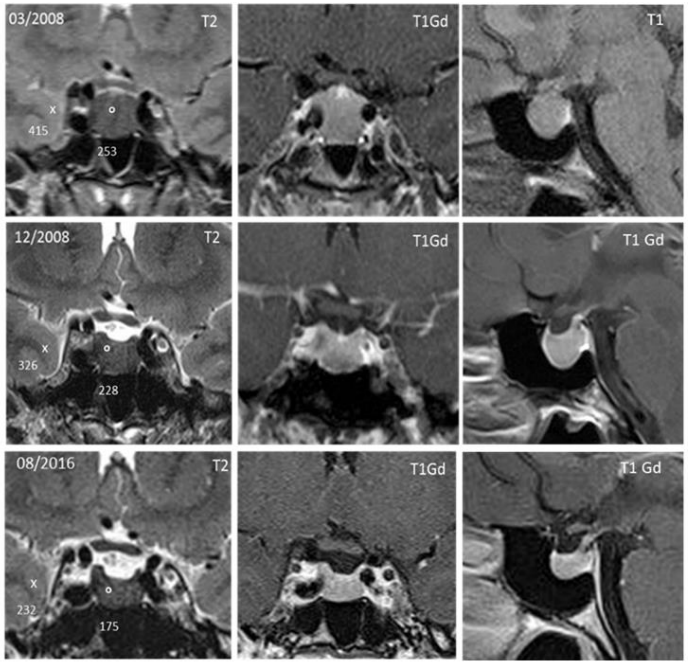

Figure 3

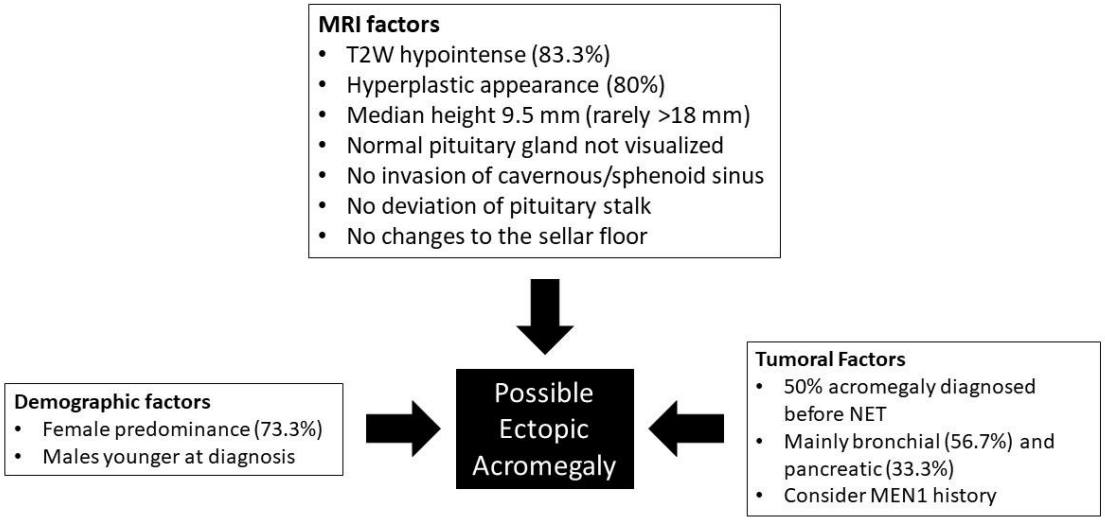

Figure 4