Acromegaly induced by ectopic secretion of GHRH: A review 30 years after GHRH discovery

Acromégalie par sécrétion ectopique de GHRH : revue de la littérature 30 ans après la découverte du GHRH

Françoise Borson-Chazot *, Laetitia Garby , Gerald Raverot , Francine Claoustrat , Véronique Raverot , Geneviève Sassolas , GTE group

Laboratoire d'hormonologie, fédération d'endocrinologie, hospices civils de Lyon, groupement hospitalier Lyon-Est, 59, boulevard Pinel, 69677 Bron cedex, France

Abstract

Ectopic acromegaly is very rare and since the discovery of growth hormone-releasing hormone (GHRH), 30 years ago, only 74 cases have been reported in the literature. Except for a recent French series of 21 cases, most of them were case reports. The present review summarizes the current knowledge on clinical presentation, diagnosis and prognosis. Tumors secreting GHRH are neuroendocrine tumors, usually well differentiated and mainly from pancreatic or bronchial origin. They are usually large and easy to localize using TDM and somatostatin receptor scintigraphy. Clinical presentation is an acromegaly of variable intensity, whose features are similar to that of a somatotropic adenoma. Pituitary may be normal or enlarged at MRI which may be difficult to interpret especially in MEN1 patients where the association of a microprolactinoma to a pancreatic tumor secreting GHRH may be misleading. GHRH plasmatic measurement has an excellent specificity for the diagnosis, using a threshold of 250 to 300 ng/L and is a good tool for follow-up of patients after treatment. These tumors have a good overall prognosis, even in metastatic forms which represent 50% of cases. Surgical approach is recommended and, when a complete tumoral resection is feasible, results, in most patients, in long-lasting remission. In such cases, GHRH concentration is normalized and its increase is an accurate indicator of recurrence. In uncured patients, somatostatin analogs control GH secretion but inhibit, only partially, GHRH secretion. MEN1 mutation should be systematically investigated in patients with a pancreatic tumor.

© 2012 Elsevier Masson SAS. All rights reserved.

Résumé

L’acromégalie par sécrétion ectopique de growth hormone-releasing hormone (GHRH) est très rare et 30 ans après la découverte du GHRH, 74 cas, seulement, ont été rapportés dans la littérature. En dehors d’une série française récente de 21 patients, il s’agit de cas cliniques isolés. Les tumeurs sécrétant GHRH sont des tumeurs neuro-endocrines, généralement bien différenciées, le plus souvent d’origine pancréatique ou bronchique. Elles sont habituellement volumineuses et faciles à localiser par le scanner et la scintigraphie des récepteurs pour la somatostatine. Le mode découvert est habituellement une acromégalie, d’intensité variable, dont les manifestations cliniques sont semblables à celles observées au cours des acromégalies par adénome somatotrope. L’hypophyse est normale ou hyperplasique à l’IRM, parfois pseudo-adénomateuse et l’interprétation de l’imagerie peut être difficile. Dans les NEM1, l’association d’un microprolactinome à une tumeur pancréatique sécrétant du GHRH peut être particulièrement trompeuse. Lorsque l’imagerie hypophysaire est douteuse, la détermination de la concentration plasmaticque de GHRH est un outil précieux du diagnostic dont la spécificité est excellente pour un seuil de 250 à 300 ng/L. Le pronostic est globalement bon même dans les formes métastatiques qui représentent près de 50% des cas. L’approche chirurgicale est recommandée et permet lorsque la résection est complète des rémissions très prolongées. La concentration plasmaticque de GHRH est alors normalisée et son ascension traduit une récidive. Les analogues de la somatostatine contrôlent la sécrétion de GH, mais ne normalisent pas celle du GHRH. Une recherche de NEM1 doit être systématique en cas de tumeur pancréatique.

© 2012 Elsevier Masson SAS. Tous droits réservés.

* Corresponding author.
E-mail address: francoise.borson-chazot@chu-lyon.fr (F. Borson-Chazot).

0033-4266/S — see front matter © 2012 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ando.2012.09.004
1. Introduction

Tumoral secretion of growth hormone-releasing hormone (GHRH) by an endocrine tumor is a rare cause of acromegaly, accounting for less than 1% of cases. Since the discovery of GHRH in 1982, 53 cases have been described in the literature mainly as case reports [1–3]. We recently reported 21 additional cases from a large multicentric retrospective French study [4]. This review summarizes the current knowledge on this pathology with special attention to the interest of GHRH determination for diagnosis and long-term follow-up and to underline the particularities of ectopic acromegaly in the context of MEN1.

2. History of growth hormone-releasing hormone (GHRH) discovery and actual perspectives

The existence of a peptide stimulating GH secretion has been suggested as early as 1959, however, research remained, inconclusive during a long period, and GHRH was only, isolated and characterized in 1982, simultaneously by two teams from human pancreatic tumors that caused acromegaly [5,6].

The first patient was a 55-year-old French male, living in Lyon, operated 16 years earlier, for a well-differentiated thymic tumor. He had an acromegaly without evidence of a pituitary adenoma. Alteration of health status and resistance to medical treatment led to the hypothesis of the tumoral secretion of a factor stimulating GH secretion. A large pancreatic tumor of 25 cm diameter was identified from whom Roger Guillemin identified three peptides, a main form of 44 amino acids (GHRH 1-44) and two reduced forms of 37 and 40 amino acids corresponding to degradation products of GHRH 1-44 by a proteolytic process [5,7]. The three forms were biologically active on GH secretion. It was shown that biological activity of GHRH lies in the 29 first residues of the N-Terminal part and that it was rapidly inactivated in plasma, in a 3-44 form, by a dipeptidylaminopeptidase [8,9].

At the same time, GHRH 1-40 was also isolated in USA by Vale’s and Thorner’s groups from another pancreatic tumor, in a 21-year acromegalic female, previously operated with the histopathological diagnosis of pituitary hyperplasia [6,10,11].

GHRH 1-40 and 1-44 were, then, isolated in human hypothalamus and their sequences were found identical to that of the peptides isolated in pancreatic tumors [12,13]. It was shown that hypothalamic GHRH, secreted in the portal system, interacted with pituitary GH cells via a 47 kDa receptor (423 AA, seven domains) coupled to G proteins to regulate the release of growth hormone from the pituitary.

Thirty years after GHRH discovery, research remains very active. Selective agonists and antagonists of GHRH have been synthesized and potential therapeutic applications are promising. Indeed, in addition to its endocrine role, GHRH may act as a growth factor. It is expressed in various tumors and may be involved in the pathogenesis and growth of cancers. Antagonists of GHRH are, currently, under investigation as anti-cancer agents. Their anti-tumor effect may be mediated through direct mechanisms such as an inhibition of the secretion of paracrine IGF1 from the tumors and/or a blockade of the action of autocrine GHRH in the tumors [14,15]. GHRH is also a regulator of important physiologic processes such as the metabolism of reactive oxygen and production of nitrogen species and GHRH agonists have been shown to contribute to the recovery of heart tissue after myocardial infarction and to stimulate the proliferation of pancreatic islets after transplantation in animals [16,17].

3. Characteristics of growth hormone-releasing hormone (GHRH) secreting tumors

3.1. Characteristics of tumors responsible for ectopic acromegaly

As shown in Table 1, GHRH secreting tumors are more frequent in women who represent 60% of cases. Median age at diagnosis is 39 years but ranges from adolescence to elderly. Gastro-enteropancreatic neuroendocrine tumors and bronchial carcinoids represent more than 90% of cases. Pheochromocytomas or paragangliomas have been reported in a small proportion of cases, occult tumors are rare accounting for only 3% of cases. Van den Bruel in a review of 51 cases reported 66% of carcinoid tumors (of bronchial origin in 79% of cases) and 28% of pancreatic tumors [18]. In the French series, tumoral sites were similar but the proportion of pancreatic tumors was 57%, greater than previously reported [4]. Although a variable size, tumors were large in most cases with a median diameter of 55 mm, non-significantly smaller in recent cases. All tumors were well-differentiated neuroendocrine tumors and bronchial carcinoids were mostly of the typical type [4]. Bronchial

<table>
<thead>
<tr>
<th>Reported cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years) (n=70)</td>
</tr>
<tr>
<td>39 (14–77)</td>
</tr>
<tr>
<td>Sex F/M (n=70)</td>
</tr>
<tr>
<td>41/29</td>
</tr>
<tr>
<td>Tumor site (n=74)</td>
</tr>
<tr>
<td>Lung: 39 (Bronchial carcinoids = 36/39)</td>
</tr>
<tr>
<td>Pancreas: 25</td>
</tr>
<tr>
<td>Pheochromocytoma: 3</td>
</tr>
<tr>
<td>Thymic carcinoid: 1</td>
</tr>
<tr>
<td>Intestinal carcinoid: 4</td>
</tr>
<tr>
<td>Occult: 2</td>
</tr>
<tr>
<td>Tumor diameter (mm) (n=49)</td>
</tr>
<tr>
<td>55 (10–250)</td>
</tr>
<tr>
<td>Metastases at diagnosis (n=62)</td>
</tr>
<tr>
<td>31/62 (50%)</td>
</tr>
<tr>
<td>MEN1 mutation</td>
</tr>
<tr>
<td>19/25 pancreatic tumors</td>
</tr>
<tr>
<td>GHRH (ng/L) (n=55)</td>
</tr>
<tr>
<td>100–145,000; median: 860</td>
</tr>
<tr>
<td>Pituitary aspect at MRI (n=63)</td>
</tr>
<tr>
<td>Normal: 12</td>
</tr>
<tr>
<td>Hyperplasia: 38</td>
</tr>
<tr>
<td>Adenoma: 13</td>
</tr>
</tbody>
</table>
Tumor types expressing growth hormone-releasing hormone (GHRH) in vitro

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Proportion of tumors expressing GHRH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine tumors:</td>
<td>25%</td>
</tr>
<tr>
<td>Pheochromocytomas and paragangliomas: 19/39 (48%)</td>
<td></td>
</tr>
<tr>
<td>Medullary thyroid carcinomas: 6/28 (21%)</td>
<td></td>
</tr>
<tr>
<td>Pancreatic tumors: 28/102 (27%)</td>
<td></td>
</tr>
<tr>
<td>Carcinoid tumors: 10/78 (14%)</td>
<td></td>
</tr>
<tr>
<td>Small cells lung carcinomas: 10/58 (26%)</td>
<td></td>
</tr>
<tr>
<td>Parathyroid adenoma: 0/10</td>
<td></td>
</tr>
<tr>
<td>Non-endocrine tumors:</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

carcinoids usually aroused from the principal or segmentar bronchial and were peripheral in only 10% of cases [19]. Pancreatic tumors were large, in most cases, arising from the caudal part of the pancreas, which may contribute to a delayed diagnosis [1,2]. They may be multi-secretant and, in the review by Van der Bruel, seven out of 14 pancreatic tumors secreted, at least, one other hormone: insulin in four cases, gastrin in three, somatostatin in two, pancreatic polypeptid in one. An increase in ACTH levels was also observed in three cases [18].

MEN1 was very frequent in cases of pancreatic tumors and was found in 19 out of the 25 reported cases (Table 1). Thus, MEN1 mutation should be investigated in all patients presenting with a pancreatic tumor secreting GHRH [4]. Tumors were metastatic at diagnosis in 50% of cases, especially when pancreatic. Metastatic sites were mainly liver, lung and bones.

3.2. Growth hormone-releasing hormone (GHRH) expression in tumoral tissues

GHRH expression was investigated in different tumor types. As shown in Table 2, GHRH expression was found in 25% of endocrine tumors, especially in pheochromocytomas, gastroenteropancreatic tumors and small cells lung carcinomas and rarely, in non-endocrine tumors [20–24]. Acromegaly was a rare feature in these patients. It has been suggested that endocrine tumors were able to synthesize GHRH but not to secrete it and/or that immuno-reactive GHRH may correspond to truncated forms with reduced biological activity [20–24]. Clinical manifestations of acromegaly being insidious, tumors may be also operated before the clinical expression of acromegaly. In this hypothesis, the incidence of ectopic acromegaly may be under estimated. Moreover, the potential consequences of GHRH expression on tumor growth and proliferation are, currently, under investigation [15].

4. Clinical and hormonal presentation of ectopic acromegaly

An acromegaly of variable intensity revealed the disease, in most cases. Clinical and hormonal manifestations were similar to that of GH secreting pituitary tumors with increased levels of GH and IGF1 and a lack of suppression of GH under oral glucose tolerance test (OGTT). The potential interest of hormonal tests has been largely investigated with disappointing results [25,26]. There was no difference in GH response to TRH stimulation, insulin tolerance test, bromocriptine or somatostatin administration. The GH response to exogenous GHRH 1–44 may be more discriminant since, by contrast with patients presenting a GH secreting pituitary tumor, there was usually no response in ectopic acromegaly.

A moderate hyperprolactinemia is frequent [1–4]. In the review by Sano, it was present in 16 out of 30 cases, without any relation with MEN1 status [2]. Its etiology remains unclear. Hyperprolactinemia may be a consequence of pituitary hyperplasia responsible for a compression of the stalk or may be driven by GHRH hypersecretion. Nevertheless, this is a confusing factor, since it may suggest a GH-PRL secreting pituitary tumor.

Rarely, other symptoms, such as hypoglycaemia or peptic ulcer, may be present in multi-secretant tumors [1–4]. Finally, some cases were discovered by systematic screening in a context of personal or familial history of endocrine tumors [4].

5. Consequences of growth hormone-releasing hormone (GHRH) hypersecretion on pituitary

5.1. Pituitary features in patients with ectopic acromegaly

The hallmark of ectopic acromegaly is pituitary hyperplasia related to prolonged GHRH hypersecretion. A reversion is usually observed after treatment of the primary tumor. Pituitary aspect may be variable at MRI. As shown in Table 1, from 64 reported cases, MRI was interpreted as hyperplastic in 38 cases, normal in 12 and adenomatous in 13. Indeed, the distinction between hyperplasia and adenoma may be difficult. This emphasizes the need for expert lecture of pituitary MRI by an experienced radiologist. In the French series, four out of the five patients with a suspicion of adenoma underwent trans-sphenoidal surgical resection [4]. Pituitary was found hyperplastic at histology and none patient was cured. An ectopic acromegaly was finally suspected because of the lack of evidence of a pituitary adenoma in eight cases, persistent acromegaly after surgery in four cases and a familial context of endocrine tumor in nine cases. However, in two MEN1 patients, a small microprolactinoma was found at surgery. In these patients, the association of an ectopic acromegaly to a microprolactinemia may be misleading and a GHRH determination should be systematic in case of acromegaly.

5.2. Consequences of prolonged growth hormone-releasing hormone (GHRH) stimulation on pituitary morphology

The question of whether prolonged GHRH hyperstimulation may induce the occurrence of a somatotropic adenoma has been long-lasting matter of debate [1–3]. Indeed, the association of hypothalamic ganagiotomas secreting GHRH to somatotropic adenomas suggests that a chronic GHRH hyperstimulation may
result in a progressive transformation of pituitary hyperplasia in a somatotropic adenoma [27]. Moreover, when GHRH is over-expressed in transgenic mice, somatotropic adenomas may be observed [28]. It has been suggested that hyperstimulated pituitary cells may be more prone to additional genetic alterations leading to neoplastic transformation.

However, in man, adenomatous transformation remains exceptional [29,30]. Nasr et al. reported one case of GHRH secreting tumor associated with both, pituitary hyperplasia and somatotropic adenoma [30]. The patient presented a cerebral metastasis producing, locally, large amounts of GHRH and a possible paracrine effect favoring the adenomatous transformation was suggested. In a MEN1 patient, a somatotropic adenoma was associated to a pancreatic tumor. In this case the inactivation of the MEN1 gene may have participated to the neoplastic transformation during prolonged GHRH hyperstimulation [29].

6. Performances of growth hormone-releasing hormone (GHRH) determination for diagnosis

Plasmatic GHRH determination is a precious tool for the diagnosis when an ectopic acromegaly is suspected [31,32].

GHRH levels have been shown undetectable (< 30 ng/L) in normal subjects and constantly low in acromegaly from pituitary origin as well as in patients with hypothalamic tumor secreting GHRH [3,31,33].

By contrast, high GHRH concentrations have been evidenced in all patients with an ectopic acromegaly [1–4]. As shown on Table 1, GHRH ranged from 100 ng/L to 145,000 ng/L with a median value of 860 ng/L. In most patients, GHRH was over 250 ng/L with GHRH between 100 and 250 ng/L in only three patients. In the French series, based on GHRH determinations performed in France since 25 years, from 25 pathological results, only one false-positive could be identified in a patient with sepsis and acute renal failure. This confirms the excellent specificity of GHRH determination for a current threshold of 250 ng/L.

The interpretation of intermediate values comprised between 30 and 250 ng/L is more difficult. Is it physiological hypothalamic GHRH or a minor secretion of GHRH by an occult tumor? In such cases, when conventional imaging does not evidence a tumor, one may suggest to control the evolution of plasmatic GHRH, especially in the context of personal or familial history of endocrine tumor. Indeed, in the French series, regular GHRH determination in a young MEN1 patient showed progressively increasing values. When plasmatic GHRH reached 250 ng/L, IGF1 became modestly elevated for age and imaging revealed a 30 mm pancreatic tumor which was probably already present for some years.

GHRH concentration did not differ according to tumor site or tumoral extension [4]. This means that GHRH determination cannot be used to assess the extent of disease. This could be explained by different degrees of differentiation of tumor cells or by differences in the proportion of GHRH secreting cells in tumors. Also, there is, only, a weak relation between IGF1 and GHRH (Fig. 1) which may suggest that circulating GHRH is partially without biological activity [33].

Fig. 1. Relation between growth hormone-releasing hormone (GHRH) concentration and IGF1 from the French series [4]. Only, a weak correlation was observed \( (R^2 = 0.476; \ p = 0.044) \) suggesting that circulating GHRH is partially inactive.

7. Localisation of the tumor secreting growth hormone-releasing hormone (GHRH)

In most cases, tumors are large at diagnosis and easily identified by conventional imaging. TDM has an excellent sensitivity estimated to 86% in the French series (Fig. 2) and endoscopic ultrasonography was necessary in only two cases of pancreatic tumor [4]. Tumors are usually well differentiated and express somatostatin receptors. Thus, somatostatin receptor

Fig. 2. Female patient, 77-year-old presenting an acromegaly with pituitary hyperplasia at MRI but no evidence of pituitary adenoma. Plasma growth hormone-releasing hormone (GHRH) was elevated at 7000 ng/L. Thoracic TDM showed a large bronchial carcinoid of 72 × 53 mm.
Fig. 3. A 55-year-old acromegalic woman with sub-normal pituitary MRI and plasma GHRH at 650 ng/L. A. Somatostatin receptor scintigraphy showed an isolated right thoracic focus confirmed by TDM. B. Somatostatin analogs administered preoperatively normalized GH but not GHRH. C. A typical bronchial carcinoid of 12 mm expressing GHRH was found at surgery which resulted in a long-lasting remission. Postoperative GHRH was undetectable (B).

scintigraphy has been shown as a good tool for the localization of tumor larger than 1 cm diameter (Fig. 3) [1–4]. Its main interest is the evaluation of tumoral spread in metastatic tumors. PET imaging has not been evaluated but its performances are probably the same as that observed in other neuroendocrine tumors of the same type and differentiation.

8. Management and prognosis

Although tumors are diagnosed at a metastatic state in 50% of cases, prognosis remains favorable. Losa [1] reported 87% of cure, after a median follow-up of 2 years, when compiling 23 operated cases. In the French series, the overall survival was 85% after a median follow-up of 5 years [4]. These data are in good accordance with the natural history of neuroendocrine tumors which are often indolent. The survival of patients presenting an endocrine pancreatic tumor, whatever his stage, has been estimated to 80% [34]. Similarly, overall survival of 80% and 60% at 5 years has been reported in typical and atypical bronchial carcinoids, respectively [35].

The only curative treatment is surgical resection of the primary tumor and when feasible of metastases. In such cases, long-lasting remission is commonly observed [1–3].

In the French series, 11 patients underwent complete tumoral resection, associated with a resection of hepatic metastases in three cases [4]. Only one presented a further hepatic recurrence which was successfully operated on.

When complete surgical resection is not feasible because of a large metastatic spread or a severe alteration of health status, somatostatin analog therapy is instituted. The treatment has no significant effect on tumoral mass but normalizes IGF1 levels in almost all cases, which is very important since GH hypersecretion is, per se, an important mortality risk factor. By contrast, GHRH secretion is reduced but never normalized [4,14,36–38]. Thus, GHRH measurement remains informative in acromegalic patients treated by somatostatin analogs. This suggests that they act mainly on pituitary by reducing GH secretion and tumoral volume with only limited effect on the primary tumor. Metastatic progressive tumors are treated with the conventional anti-neoplastic agents used in neuroendocrine tumors (chemotherapy, chemoembolization of liver metastases, radiotherapy and recently, targeted therapies). In the French series, from the nine non-operated patients, only three patients deceased during follow-up and prolonged survival were observed in others [4].

GHRH determination is an accurate indicator of patient’s status after surgery. In our series, GHRH levels were undetectable in patients in remission and remained elevated in all patients with persistent disease. Moreover, an increase in GHRH levels was the first manifestation of recurrence in two patients that was secondarily evidenced by imaging [4]. Thus, during the postoperative follow-up, GHRH should be considered for use as a monitoring tool.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgements

We thank all the contributors to the French nationwide study: Pr Philippe Chanson, Pr Antoine Tabarin, Pr Philippe Caron, Pr Vincent Rohmer, Pr Olivier Chabre, Pr Jean-Louis Sadoul, Pr Sophie Christin-Maire, Dr Arnaud Murat, Pr Fabricre Bonnet, Dr Helene du Boullay, Dr I Nakib, Dr Gwenaelle Arnaud and the GTE for financial support.
References


