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1 **Pituitary MRI Features in Acromegaly due to Ectopic GHRH Secretion from a Neuroendocrine**  
2 **Tumor: Analysis of 30 cases**

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11

12 **Short title:** MRI characteristics of ectopic acromegaly

13

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60

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62

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64

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73 **Abstract**

74 Context: Ectopic acromegaly is a consequence of rare neuroendocrine tumors (NET) that secrete growth  
75 hormone releasing hormone (GHRH). This abnormal GHRH secretion drives growth hormone (GH)  
76 and insulin-like growth factor 1 (IGF-1) excess, with a clinical presentation similar to classical pituitary  
77 acromegaly. Identifying the underlying cause for the GH hypersecretion in the setting of ectopic GHRH  
78 excess is, however, essential for proper management both of acromegaly and the NET. Owing to its  
79 rarity, the imaging characteristics of the pituitary in ectopic acromegaly have not been analyzed in depth  
80 in large series.

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

83 Design: Multicenter, international, retrospective

84 Setting: Tertiary referral pituitary centers

85 Patients: 30 ectopic acromegaly patients due to GHRH hypersecretion

86 Intervention: None

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

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

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

96 **Introduction**

97 Acromegaly is a rare endocrine disorder with an estimated prevalence of 10.5 cases per 100000  
98 individuals <sup>1</sup>. It is usually due to growth hormone (GH) hypersecretion from a pituitary adenoma. Less  
99 than 1% of cases of acromegaly are secondary to ectopic secretion of growth hormone releasing  
100 hormone (GHRH), usually from a bronchial or pancreatic neuroendocrine tumor (NET), although other  
101 sources of abnormal GHRH secretion have been described (e.g. hypothalamic gangliocytomas <sup>2</sup>).

102 The rare nature of ectopic acromegaly can complicate its diagnosis and pituitary surgery can be  
103 performed inadvertently. The symptoms of ectopic acromegaly and the GH and insulin-like growth  
104 factor 1 (IGF-1) levels are not always different from those encountered in classical acromegaly. While  
105 GHRH measurement can greatly aid the differential diagnosis, it is not routinely assessed at diagnosis  
106 in acromegaly. Functional imaging techniques, such as somatostatin receptor scintigraphy, might reveal  
107 the presence of a neuroendocrine tumor, but again, these techniques would not be useful in the routine  
108 work-up of the >99% of patients with pituitary adenoma-related acromegaly.

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

120 **Methods**

121

122 We performed a Medline search of the English literature using the terms ‘ectopic’, ‘acromegaly’ and  
123 ‘GHRH’ to identify publications dealing with ectopic acromegaly since the advent of MRI in 1992. As  
124 previous studies did not systematically report T2W series (only gadolinium enhanced T1W series were  
125 typically reported), we contacted authors of publications to obtain additional T2W sequences, if  
126 available. Additionally, an international case finding process was performed at tertiary referral centers  
127 to identify previously unpublished cases of acromegaly secondary to pathologically-proven ectopic  
128 GHRH secretion.

129 Only cases in which T2W series were available were included in the analysis. For these patients,  
130 demographic, clinical, biochemical, histological data were gathered, as well as information regarding  
131 treatment of the acromegaly and of the underlying NET, and the responses to treatment. Diagnostic  
132 pituitary MRI examinations, as well as follow-up MRIs, whenever available, were analyzed.

133 Diagnosis of acromegaly was established in each medical center based on generally-employed criteria:  
134 an elevated IGF-1 level above the normal values for age and sex at the local laboratory and, in most  
135 cases, non-suppressible GH values during an oral glucose tolerance test (OGTT). Whenever available,  
136 GHRH values were reported. GHRH measurements were performed primarily at the laboratories of  
137 two coauthors at centers in Lyon, France (V.R.) and Munich, Germany (M.B.). These two groups  
138 regularly exchange samples to maintain consistency between the methods used. In Lyon, the assay  
139 used was described in Girard P et al <sup>8</sup>. In that assay plasma GHRH was measured using an in-house  
140 double-antibody RIA. The intra-assay CV is <6%, and inter-assay CV is <15%. In normal controls, the  
141 circulating GHRH concentration was below the detection limit of the assay (<60 ng/liter). In Munich,  
142 GHRH plasma concentrations were measured by fluorescence immunoassay (FIA) as described in  
143 Schopohl J et al <sup>9</sup>. Sensitivity was 100 pg/ml, intra-assay CV<11%, and inter-assay CV<15%. GHRH  
144 values for the patients included in our study were above the cut-off of the assay (generally 60 to 100  
145 ng/l), whereas in pituitary acromegaly, GHRH values are expected to be suppressed.

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

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

155 All the patient information was encoded as anonymous data. Statistical analyses were performed using  
156 the R statistical package <sup>12</sup>. Data were plotted and assessed for normal distribution. Since none of the  
157 variables showed a normal distribution, population spread was described using median and interquartile  
158 ranges (25<sup>th</sup> and 75<sup>th</sup> percentiles). Count variables were tested with the Chi-square test. Continuous  
159 variables were compared using the Mann-Whitney and Kruskal-Wallis tests.



160 **Results**

161 Patient characteristics

162 We included 17 cases previously reported in the literature that had been investigated with T2W series  
163 either at diagnosis (14 cases) or during follow-up (3 cases). The international case-finding approach  
164 identified a further 13 unpublished cases, bringing the total to 30 cases of ectopic acromegaly with an  
165 MRI examination that included T2W series (Table 1). There were 22 females and eight males. The  
166 median overall age at diagnosis of acromegaly was 42 years (Q1: 35, Q3: 55); the median age of  
167 diagnosis was younger in males (34.5 years) than females (50.5 years) ( $p = 0.03$ ).

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

173 Median IGF-1 levels at diagnosis were 2.8 x ULN (Q1: 2.5, Q3: 3.6). Median random GH levels were  
174 16  $\mu\text{g/l}$ . GHRH was assessed in 24 patients, with values ranging from 82 to >17 000 ng/l. We found no  
175 relationship between GHRH values and IGF-1 levels, nor between GHRH values and the presence of a  
176 metastatic tumor. Four patients had previously diagnosed *MEN1* mutations, but *MEN1* gene sequencing  
177 was not performed as part of this study.

178 Twenty-three patients had surgery of the NET with disease remission in 17 cases. Pituitary surgery was  
179 performed in three patients. First-generation somatostatin receptor ligands (SRLs) were administered in  
180 16 patients (either when ectopic secretion of GHRH was not controlled after NET surgery, in patients  
181 for whom NET surgery was not performed, and in individual cases, before NET surgery).

182

183 MRI features

184 *Pre-treatment*

185 Initial pituitary MRI reports of the 17 previously published cases described pituitary hyperplasia in nine  
186 cases, a normal pituitary in four, a pituitary adenoma in two cases, pituitary apoplexy in the context of  
187 a pituitary adenoma and adjacent hyperplasia in one patient and a partially empty sella in one case. By  
188 comparing the pituitary dimensions with published reference values, we classified 14 of the cases as  
189 being consistent with hyperplasia, one had an adenoma, one had a partially empty sella and another had  
190 a borderline pituitary height. Including histological results suggestive of pituitary hyperplasia in the  
191 patient with pituitary apoplexy, the number of cases of hyperplasia rises to 15/17. After evaluation of  
192 their T2W signal, in all but two of the 17 cases the pituitary was T2-hypointense. The remaining patients  
193 correspond to the one with borderline pituitary height, who had a T2-isointense pituitary and the patient  
194 with pituitary apoplexy with a T2-hyperintense, heterogeneous pituitary. Three of the T2-hypointense  
195 pituitaries were heterogeneous, exhibiting small T2W hyperintense regions.

196

197 For the 13 unpublished cases, nine patients had pituitary hyperplasia (median pituitary height of 13 mm),  
198 one had borderline pituitary height (6 mm), two had normal pituitary glands (4 mm) and one had a  
199 partially empty sella (2 mm). The T2W signal was hypointense in ten cases, isointense in two and  
200 hyperintense in one case. The T2W signal was heterogeneous for the T2-hyperintense pituitary and also  
201 for one T2-hypointense case. The T2W signal was hypointense in 8/9 cases of hyperplasia, in the case  
202 of borderline pituitary height and in the patient with a partially empty sella. The two T2W-isointense  
203 cases corresponded to the patients with normal pituitary volumes. For the case with T2-hyperintense  
204 hyperplasia, the most likely diagnosis was metastasis, as this patient also had multiple brain metastases.  
205 Overall, among the total of 30 cases, pituitary hyperplasia was found in 24 cases with borderline  
206 increased tumor size in a further two cases. In the remaining four cases the pituitary gland height was  
207 not increased for the patient's age (either normal-sized pituitaries in two patients or partially empty sella  
208 in two other patients). The median pituitary height was 9.5 mm. Pituitary height was never more than  
209 18 mm except for one case with associated metastasis and one case with pituitary apoplexy. There was  
210 a weak negative correlation ( $r = -0.37$ ,  $p = 0.04$ ) between pituitary height and age at diagnosis with the  
211 oldest patient in the series, aged 84, having a partially empty sella.

212 T2-weighted signal was hypointense in 25/30 cases, isointense in three and hyperintense in two cases.  
213 In four cases with T2-hypointense pituitaries, small T2 hyperintense spots, probably of necrotic or  
214 hemorrhagic origin, were observed.

215 Normal pituitary gland tissue was never visualized, which differs from the situation of acromegaly due  
216 to a pituitary adenoma where normal pituitary tissue is usually compressed on one side of the sella  
217 (Figure 1). Invasion of the cavernous or sphenoid sinus was not found in any of the cases. There were  
218 no detectable changes of the sellar floor and the pituitary stalk did not appear deviated. In the few cases  
219 where dynamic imaging with gadolinium injection was performed, it showed delayed pituitary  
220 enhancement.

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

225

#### 226 *Post-treatment*

227 In 21/30 patients, MRI examinations including T2W sequences were also performed either after surgery  
228 of the NET, after pituitary surgery and/or after treatment with SRLs. The duration of SRL therapy varied  
229 from three months to 11 years. Among the patients treated with NET surgery, a follow-up MRI was  
230 available in 15/23 cases. Pituitary hyperplasia shrank in 13 cases, whereas one had a stable volume and  
231 another had an increase in pituitary volume. In this latter case, pituitary volume increased due to the  
232 enlargement of the associated collision pituitary adenoma in a MEN1 patient. Pituitary T2W signal

233 remained hypointense, although the hypointensity was less pronounced than at diagnosis in 11 cases and  
234 changed from hypointense to isointense in four. In these last four cases, the patients were considered  
235 cured and all biological values normalized. However, in four other cases in which remission was  
236 obtained, the T2W did not change appreciably in hypointensity versus the diagnostic MRI.  
237 Among the eight patients with follow-up MRIs who received SRL treatment and were not cured with  
238 NET surgery or in whom NET surgery was not performed, pituitary shrinkage was found in six  
239 patients. One patient had a stable pituitary volume. Increase of tumor volume was found in one patient  
240 suspected of having both pituitary metastasis and hyperplasia, with a T2-hyperintense pituitary mass  
241 corresponding to the pituitary metastasis. The six-month follow-up MRI of this last patient revealed  
242 pituitary tumor volume increase despite maximal medical treatment. The diagnosis of pituitary  
243 metastasis was supported by the appearance of multiple brain metastases. Except for that patient, the  
244 T2-weighted signal on follow-up MRI in SRL-treated patients was hypointense, and in only one case  
245 was the hypointensity less pronounced than at diagnosis.

246 **Discussion**

247

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

254 Acromegaly secondary to GHRH hypersecretion from a NET has similar clinical and biological  
255 characteristics to those of acromegaly due to GH-secreting pituitary adenomas. Patients diagnosed with  
256 ectopic acromegaly are only slightly younger (36-41 years) than patients with pituitary acromegaly (45  
257 years) <sup>3,13,14</sup>. Female patients are more frequent among ectopic acromegaly patients; in the largest series  
258 published, over 2/3 patients were females, which mirrors our findings <sup>3,13</sup>. The delay between first  
259 acromegaly symptoms and diagnosis of acromegaly is similar in ectopic and pituitary acromegaly, at  
260 around eight years. IGF-1 values at diagnosis are also similar in pituitary and ectopic forms of  
261 acromegaly, with median values around 2.6-2.7-fold ULN, which was also seen in the current series. As  
262 is the case with somatotropinomas being larger in younger patients <sup>14</sup>, in ectopic acromegaly there also  
263 seems to be a correlation, albeit weak in our series, between age at diagnosis and pituitary height, with  
264 younger patients developing greater hyperplasia.

265 Differentiating between pituitary hyperplasia and adenoma is an important step in the assessment of  
266 acromegaly and in identifying the origin of the hormonal disturbance as pituitary GH hypersecretion or  
267 ectopic, extra-pituitary GHRH overproduction. It is generally considered that pituitary MRI does not  
268 provide enough evidence for a definitive diagnosis of ectopic acromegaly. In a series of 20 patients with  
269 ectopic acromegaly and available pituitary imaging, Garby et al. found eight cases of hyperplasia, five  
270 pituitary adenomas, five cases with a normal pituitary and two with a microcystic lesion <sup>13</sup>. A series of  
271 98 cases of ectopic acromegaly from the English language literature published between 1974 and 2011,  
272 many of which were only explored by computed tomography, found 41 cases with an enlarged pituitary,  
273 27 cases of adenoma, two with empty sella, 18 normal pituitaries and two microcystic lesions <sup>3</sup>. Of the  
274 98 cases, 30 patients were operated on for presumed somatotropinomas. Correct identification of the  
275 source of acromegaly (pituitary or ectopic) is then of major importance to avoid unnecessary pituitary  
276 surgery.

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

281 66-year-old man, but the mean height at this age and sex is nearly 2 mm less according to one reference  
282 series, thereby suggesting hyperplasia. Differential diagnosis between pituitary hyperplasia and pituitary  
283 adenoma can be subtle. In our series, hyperplasia was symmetrical with a pituitary height less than 20  
284 mm and a sellar floor that was unchanged or had minor symmetrical changes. Clinical symptoms of  
285 optic chiasm compression are not to be expected with moderate hyperplasia that usually does not reach  
286 the optic chiasm. In our series, there was no invasion of the cavernous or the sphenoid sinuses. An  
287 important point is that, unlike what is generally found in patients with pituitary adenomas, normal  
288 pituitary tissue was not identified (Figure 1). Applying these criteria, no MRI pattern similar to a  
289 pituitary adenoma was found in our series of 30 patients, apart from one patient with a very likely  
290 metastasis that masked the pituitary hyperplasia, from one MEN1 patient with a collision lesion and  
291 from a patient with pituitary apoplexy, having a somatotropinoma and hyperplasia on histological  
292 analysis. Regarding this latter patient, he had already had a cerebral MRI for an unrelated reason 20  
293 months prior to the diagnosis of apoplexy and at the time, the pituitary was already slightly hyperplastic  
294 and T2-hypointense. This indicates that chronic stimulation of the somatotrope cells by GHRH can  
295 induce adenoma formation, as already described in a genetic context<sup>15</sup>. However, this phenomenon is  
296 most likely rare and potentially only induced by marked GHRH hypersecretion, as we have not identified  
297 other similar cases of adenomas detectable by MRI in our series. Of course, very small adenomatous  
298 changes cannot be excluded without histological analyses.

299 In recent years, several studies have shown an important role for T2-weighted MRI sequences in the  
300 assessment of acromegaly<sup>4,6,16,17</sup>. T2-weighted adenoma signal permits discrimination between different  
301 types of somatotropinomas in terms of the magnitude of GH secretion, adenoma characteristics (size,  
302 local extension, invasiveness), response to SRL and, most likely, histological features<sup>5,7</sup>. However, T2-  
303 weighted series of pituitary MRIs have never been previously analyzed in the diagnosis of GHRH-  
304 related acromegaly. In our series, 25/30 patients had T2-hypointense pituitaries and among them, 22  
305 pituitaries were hyperplastic. Only two patients had T2-hyperintense pituitaries and these patients  
306 suffered from either the extremely rare occurrence of associated pituitary metastasis or pituitary  
307 apoplexy. Three patients had T2-isointense pituitaries and these were patients with normal or only  
308 slightly enlarged pituitaries. The explanation for why densely granulated adenomas as well as pituitary  
309 hyperplasia due to GHRH hypersecretion appears T2 hypointense is still unknown. According to  
310 Hagiwara<sup>16</sup>, the amounts of amyloid, fibrous tissue and iron contained in somatotropinomas seem to  
311 have little influence on signal intensity. Densely granulated adenomas have numerous secretory granules  
312 while other pituitary adenomas have few or no secretory granules. It could be that protein-rich secretory  
313 granules influence signal intensity on T2-weighted images. T2-weighted pituitary hypointensity returns  
314 to isointensity in a few cases after successful NET surgery along with pituitary shrinkage (Figure 2).  
315 However, for unknown reasons, T2-weighted pituitary signal remains hypointense in other patients for  
316 as long as ten years of follow-up despite complete normalization of all biological parameters and

317 remission of the NET (Figure 3). This persistence of the T2-hypointense signal argues in favor of  
318 GHRH-driven alterations in the ultrastructure of the pituitary somatotrope cells that are partially  
319 irreversible.

320 While surgical excision of the GHRH-secreting NET along with resection of metastases is the ideal  
321 treatment, SRLs have also shown some efficacy both in terms of tumor volume reduction and on  
322 biochemical responses in terms of GHRH, GH and IGF-1 lowering<sup>18</sup>. In our series, most patients on  
323 SRLs were found to exhibit pituitary shrinkage, while T2 hypointensity most often remained similar in  
324 magnitude to that seen at diagnosis. Overall, it seems that a relationship exists between the change of  
325 T2-hypointensity and the biological response to treatment of the GHRH-induced pituitary hyperplasia.

326 Limitations of the study include the lack of complete availability of retrospective quantitative  
327 measurement of T2W signal. However, we have previously demonstrated that a visual approach through  
328 comparison of pituitary versus gray matter T2-weighted signal represents a valid evaluation<sup>4</sup>.

### 329 **Conclusions**

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

342

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347

348 Data Availability

349

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

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431

432

433 **Table 1.** Patient characteristics of patients with ectopic acromegaly included in the series. Cases  
434 marked with an \* have previously been reported in the literature. NET – neuroendocrine tumor, SRL  
435 – 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	YES	NO
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

436

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

444

445 **Figure 2.** A. Slightly heterogeneous, T2-hypointense pituitary hyperplasia with T2-hyperintense foci in  
446 a 59-year-old female patient diagnosed with acromegaly (IGF-1 2.7 x ULN) due to a GHRH-producing  
447 bronchial tumor (GHRH levels at diagnosis 17727 ng/l). B. After thoracic surgery, normalization of  
448 IGF-1 and GHRH levels with shrinkage of the pituitary and a T2W signal that has become isointense.

449

450 **Figure 3.** Evolution of the pituitary after treatment of a GHRH-producing bronchial carcinoma in a 35-  
451 year-old female patient diagnosed with acromegaly (IGF-1 3.7 x ULN). Rapid decrease in pituitary size  
452 after surgery of the bronchial carcinoma (performed in 10/2008) which led to normalization of IGF-1,  
453 with further pituitary shrinkage in time. Despite biochemical cure, the pituitary T2-weighted signal  
454 intensity remained hypointense (Region of Interest values for the pituitary and the temporal gray matter  
455 are found on each T2-weighted section). Each line presents sections from MRI performed at the same  
456 time, the first column contains T2-weighted coronal sections, the second line gadolinium-enhanced  
457 coronal sections and the third line gadolinium-enhanced sagittal sections.

458

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