The coexistence of newly diagnosed acromegaly with primary empty sella: more frequent than expected?

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Research Article

Keywords: Acromegaly, empty sella, coexistence, rare association

Posted Date: August 12th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1918956/v1

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Abstract

Purpose

We investigated the coexistence of newly diagnosed acromegaly with primary empty sella (ES), which is considered to be a rare association, and the impact of ES on the laboratory, radiological and prognostic status of acromegaly.

Methods

Acromegaly patients diagnosed and followed-up between 2012–2021 were included. Empty sella was defined as the pituitary gland and adenoma filling less than 50% of the sella turcica on preoperative T1 magnetic resonance imaging (MRI).

Results

102 acromegalic patients (45 male, 57 female, 45.5 ± 12.8 (range: 20–70 years) were included and data of a median 3 years (range: 0.5-9 years) were presented. Empty sella was detected in 19 (18.6%) patients and 4 had complete and 15 had partial ES. Although not significant, adenoma size and residual adenoma on MRI on postoperative 3rd month, and disease remission at last control were lower in acromegaly with ES than in acromegaly without ES, while the rate of female gender and remission on postoperative 3rd month were higher. While preoperative serum prolactin and nadir GH responses to OGTT were significantly lower in patients with ES, there was no difference in terms of other pituitary hormones among both groups.

Conclusion

The present study revealed the coexistence of newly diagnosed acromegaly with primary ES at a rate of nearly 20% which is more frequent than expected and this association is not rare. The presence of ES was not associated with any preoperative/postoperative pituitary hormone levels and remission status, except lower preoperative prolactin and nadir GH responses to OGTT.

Introduction

Acromegaly is a rare systemic pituitary disease characterized by growth hormone (GH) hypersecretion with typical phenotypic features. Its prevalence is 30–70 patients per million while its annual incidence is 3–4 patients per million. It is caused by a pituitary adenoma in more than 95% of cases, and very rarely by ectopic GH or growth hormone-releasing hormone secretion (GHRH) [1, 2].
Empty sella (ES) is an anatomical and radiological condition resulting from herniation of the subarachnoid space and partial or complete filling with cerebrospinal fluid (CSF) into the sella turcica [3]. Secondary ES is more frequent, and occurs as a result of shrinkage of the pituitary gland and adenoma caused by ischemic and hemorrhagic necrosis or pituitary surgery, radiotherapy and hormonal medical treatment or hypophysitis [4–6]. Primary ES is often detected incidentally and has no obvious cause. The frequency of ES varies between 5% and 7% and it has a female/male ratio of 4:1 [3, 7, 8]. Although pituitary functions are usually preserved in patients with ES, isolated hormone deficiency, hyperprolactinemia, and partial or complete hypopituitarism may be detected in up to 50% of cases [4, 9]. The coexistence of pituitary adenoma and primary ES is reported as a very rare condition [10, 11].

In the present study, we investigated the coexistence of newly diagnosed acromegaly with primary empty sella, which is considered to be a rare association, and the impact of ES on the laboratory, radiological and prognostic status of acromegaly.

**Patients And Methods**

The study approval was obtained from the Ethics Committee of Erciyes University Medical Faculty. Acromegaly patients diagnosed and followed-up between 2012-2021 were included in the study and data of a median 3 years (range: 0.5-9 years) were presented.

The diagnosis of acromegaly was based on current guidelines [12] and was accepted as serum insulin-like growth factor 1 (IGF-1) values above the reference range for age and gender and/or the lowest (nadir GH) GH value above 1 ng/mL during OGTT.

ES was defined as the pituitary gland and adenoma filling less than 50% of the sella turcica on preoperative T1 magnetic resonance imaging (MRI) [13]. The maximum height of the pituitary gland < 2 mm was considered as complete ES and higher than 2 mm was accepted as partial ES [14]. The maximum size of the pituitary adenoma was evaluated on T1 coronal sections of MRI. Pituitary adenoma size lower than 10 mm was accepted as microadenoma and ≥ 10 mm were accepted as macroadenoma. MRI assessments were performed by a radiologist experienced in neuroradiology.

The patients’ age and body mass index (BMI), serum IGF-1, prolactin and nadir GH responses to OGTT, thyroid function tests, hypothalamo-pituitary adrenal axis, gonadotropins were evaluated on the preoperative period and also on the postoperative third month and at the last control. Pituitary MRI was also obtained at each visit.

The disease remission was defined as normal serum IGF-1 values adjusted for age and gender, random serum GH values less than 2.5 ng/mL and/or nadir GH value less than 1 ng/mL [12].

**Analytical methods**

Serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, adrenocorticotropic hormone (ACTH),
cortisol, estradiol, total testosterone, growth hormone (GH) and insulin-like growth factor 1 (IGF-1) were measured using the electrochemiluminescence immunoassay (ECLIA) technique with commercially available assays (Cobas; Roche Diagnostics, Mannheim, Germany).

**Pituitary MRI protocol**

Our pituitary MRI protocol was including pre-contrast sagittal and coronal T1-weighted spin-echo sequences, axial and coronal T2-weighted images. Following the contrast administration, dynamic T1-weighted images with 2-3 mm slice thickness and 6-10 time-points, post-contrast delayed coronal and sagittal T1-weighted spin-echo sequences were obtained.

**Statistical analysis**

The data were analyzed in the SPSS version 20 (IBM Inc, USA). Shapiro-Wilk Test was used for distribution of data. Normally distributed data were shown as the mean ± standard deviation and non-normally distributed data as the median (25%–75%). Two independent samples t-tests or Mann-Whitney U test was used according to the distribution of data in two independent groups. The Chi-square test was used for the analysis of categorical data. A probability (p) value lower than 0.05 was considered statistically significant.

**Results**

102 acromegalic patients (45 male, 57 female, mean age 45.5 ± 12.8 years (range: 20–70 years) were included in the study. Empty sella was detected in 19 (18.6%) patients and 4 had complete and 15 had partial ES. Among the patients with ES, 12 (63%) were female and 7 (37%) were male. The comparisons of acromegalic patients with and without ES on the preoperative period and on the postoperative 3rd month are shown in Tables 1 and 2. The pituitary MRI of two patients with coexistence of newly diagnosed acromegaly and primary ES are shown in Figs. 1 and 2.

There was no difference between acromegalic patients with and without ES in terms of BMI, age at diagnosis, and gender. While preoperative serum IGF-1 values were similar in both groups, nadir GH responses to OGTT were significantly lower in patients with ES than in patients without ES [2.5 (1.1–3.5) ng/mL vs 6 (2.8–12.9) ng/mL, respectively, p = 0.04]. Twelve (63%) of the patients with ES had macroadenomas and 6 (32%) had microadenomas, adenoma could not be localized in one patient. There were no differences in both groups in terms of adenoma size and type. Serum TSH, FT4, FT3, basal cortisol values, the presence of secondary hypothyroidism, secondary hypoadrenalism, and secondary hypogonadism on the preoperative period were similar in both groups. Prolactin values on the preoperative period were significantly lower in patients with ES than in patients without ES (7.7 (5.5–13.5) ng/mL vs 17.6 (9.2–38.9) ng/mL, respectively, p = 0.001).

Serum TSH, FT4, FT3, IGF-1 and basal cortisol values, nadir GH responses to OGTT, presence of secondary hypothyroidism, secondary hypoadrenalism, and secondary hypogonadism on the
postoperative 3rd month were similar in both groups. Although not significant, the ratio of residual adenoma on MRI on postoperative third month was lower in patients with ES (53%) than in patients without ES (57%) and the ratio of disease remission on postoperative third month was higher in patients with ES (42%) than in patients without ES (37%). At the last control, the ratio of disease remission was lower in patients with ES (63%) compared to patients without ES (67.5%), but it was not significant.

**Discussion**

The coexistence of newly diagnosed acromegaly with primary empty sella is not a usual predictable and well-known association in clinical practice. The current literature has several case reports and very limited studies regarding this coexistence.

In the present study, primary ES was detected in 19 (18.6%) of 102 newly diagnosed acromegaly, and this was a more frequent association than expected/reported. For the first time, we have also compared the preoperative/postoperative (other) pituitary hormone levels in acromegalic patients with and without ES. We found that preoperative prolactin and nadir GH responses to OGTT were significantly lower in acromegalic patients with ES than without ES. Although it was not significant, adenoma size and residual adenoma on MRI on the postoperative 3rd month, and disease remission status at last visit were lower in acromegaly with ES than in patients without ES, while the rate of female gender and remission on postoperative 3rd month were higher in ES group.

The frequency of ES in the normal population is reported as 5–7% [3]. To the best of our knowledge, according to the results of previous three studies evaluating ES coexistence with newly diagnosed acromegaly, the prevalences were 15.4% [8], 20% (only GH positive microadenomas were included in this study) [13], and 22% [15]. According to these results, we can say that this association is not a rare coexistence.

Lui et al. [13] compared the frequency of ES in 69 GH positive microadenoma and 103 GH negative microadenoma on immunohistochemical staining. Empty sella was significantly higher in GH positive microadenoma (20% vs 3.9%, respectively). Also, Bier et al. [15] evaluated 159 GH positive adenoma, 150 GH negative adenoma and 50 healthy subjects without pituitary adenoma and found that the frequency of ES was significantly higher in GH positive adenoma (22% vs 5% vs 8%, respectively). These two studies showed that the primary ES coexistence is more frequent in newly diagnosed acromegaly than in other types of pituitary adenomas. Also, Bier et al. [15] revealed that GH positive adenoma had a higher rate of intrasellar location and lower rate of suprasellar extension than GH negative adenoma. They speculated that because of this growth pattern of GH positive adenomas, acromegaly was more frequently associated with ES than GH negative adenomas. On the other hand, Lui et al. explained the increased coexistence of ES with GH positive adenoma as the paracrine effect of GH by influencing local bone remodeling, thereby changing the bone structure in the sellar floor and clivus [13]. Another hypothesis in this regard is pituitary apoplexy [8].
Sasagawa et al. found that being female gender is associated significantly higher ES in acromegaly than acromegaly without ES (83% vs 53%) [8]. In our study, 63% of the patients with ES was female, but it was not significant. It is well known that one of the most important causes of ES is intracranial hypertension, and both diseases are female-dominated [3, 7]. We think that female dominance in acromegaly patients with ES is also caused by the nature of ES.

Sasagawa et al. detected significantly smaller adenoma size and higher intraoperative cerebrospinal fluid (CSF) leakage in acromegaly patients with ES [8], which suggest more intensive follow-up in terms of possible complications in pituitary surgeries of patients with acromegaly with ES. However, in our study, the adenoma size was lower in the ES group, although it was not significant and the follow-up of intraoperative CSF leakage was not recorded.

We found similar disease remission in the postoperative third month and at the final follow-up visit in both groups (ES + vs ES - acromegaly). In the current literature, in contrast to our data, the remission status was evaluated only by Sasagawa's study but they evaluated only in the postoperative third month and did not find a significant difference in terms of remission between the groups [8]. According to these results, it can be suggested that the presence of ES in acromegaly has no effects on the short- and long-term disease remission. However, available studies and data on this issue are very limited and studies with larger samples will be helpful.

Preoperative and postoperative other pituitary hormone levels and hormone deficiency status of patients with and without ES associated with acromegaly were compared for the first time in our study. While preoperative prolactin and nadir GH responses to OGTT were significantly lower in acromegaly patients with ES, there was no significant difference in comparison of thyroid, adrenal and gonadal axis among both groups. Although GH deficiency is most frequently seen, primary ES may be presented with endocrine disturbances such as isolated other hormone deficiencies, hyperprolactinemia or panhypopituitarism. Interestingly, hyperprolactinemia may be observed in 7–10% of cases [3, 16]. Pituitary hormone deficiency is an expected condition for ES, the significantly lower preoperative prolactin and nadir GH levels in the ES group can be attributed to this.

In conclusion, our study revealed the coexistence of newly diagnosed acromegaly with primary ES at a rate of approximately 20% which is more frequent than expected/reported. Among the acromegalic patients with ES and without ES, preoperative/postoperative pituitary hormone levels and remission status were similar, except that preoperative prolactin and nadir GH responses to OGTT were lower in the ES group. Although few hypotheses are speculated about the underlying mechanisms of the increased coexistence of acromegaly and ES, further studies on the etiopathogenesis are needed.

**Declarations**

**Acknowledgments** None

**Funding** None
Conflict of interest All authors declare no conflict of interest in the reported research.

Data availability The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval All procedures which were performed in studies with human participants followed the 1964 Helsinki Declaration the ethical standards of the national or institutional research committee and its later amendments or comparable ethical standards.

Informed consent Informed consent in this study was taken from all participants

References


Tables

Table 1. Preoperative comparison of patients according to the absence/presence of empty sella
BMI: Body mass index, IGF-1: Insulin-like growth factor 1, GH: Growth hormone, TSH: Thyroid-stimulating hormone, FT4: Free thyroxine, FT3: Free triiodothyronine, ES: Empty sella

Table 2. The comparison of patients according to empty sella presence on postoperative 3rd month

<table>
<thead>
<tr>
<th></th>
<th>ES + (n= 19)</th>
<th>ES – (n= 83)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of diagnosis (years)</td>
<td>51 (39-56)</td>
<td>43 (35-55)</td>
<td>0.36</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>30.4±5.1</td>
<td>29.8±5.8</td>
<td>0.67</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 male (37%)</td>
<td>38 male (46%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 female (63%)</td>
<td>45 female (54%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma size (mm)</td>
<td>12.5 (7-15.5)</td>
<td>14 (10-20)</td>
<td>0.11</td>
</tr>
<tr>
<td>Adenoma type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 microadenoma (32%)</td>
<td>18 microadenoma (22%)</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>12 macroadenuma (63%)</td>
<td>65 macroadenoma (78%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(An adenoma could not be localized)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-1 (ng/mL)</td>
<td>769.2±322.9</td>
<td>749.2±283</td>
<td>0.79</td>
</tr>
<tr>
<td>Nadir GH (ng/mL)</td>
<td>2.5 (1.1-3.5)</td>
<td>6 (2.8-12.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>TSH (μU/mL)</td>
<td>1.1 (0.8-2)</td>
<td>1.4 (0.9-2)</td>
<td>0.41</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>1.2±0.2</td>
<td>1.2±0.3</td>
<td>0.19</td>
</tr>
<tr>
<td>FT3 (pg/mL)</td>
<td>3.4 (3.2-3.8)</td>
<td>3.4 (3.1-3.9)</td>
<td>0.97</td>
</tr>
<tr>
<td>Cortisol (μg/dL)</td>
<td>10.8 (8.1-13)</td>
<td>10.1 (7.2-15)</td>
<td>0.13</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>7.7 (5.5-13.5)</td>
<td>17.6 (9.2-39)</td>
<td>0.001</td>
</tr>
<tr>
<td>Secondary Hypothyroidism</td>
<td>1 (%5)</td>
<td>10 (%12)</td>
<td>0.53</td>
</tr>
<tr>
<td>Secondary Hypoadrenalism</td>
<td>2 (%10.5)</td>
<td>9 (%11)</td>
<td>0.61</td>
</tr>
<tr>
<td>Secondary Hypogonadism</td>
<td>6 (%32)</td>
<td>27 (%32.6)</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>ES + (n=19)</td>
<td>ES – (n=83)</td>
<td>P Value</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>---------</td>
</tr>
<tr>
<td>IGF-1 (ng/mL)</td>
<td>240 (182-449)</td>
<td>273 (181.5-395)</td>
<td>0.7</td>
</tr>
<tr>
<td>Nadir GH (ng/mL)</td>
<td>2 (2.1-3.8)</td>
<td>1.5 (0.8-4.5)</td>
<td>0.7</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>0</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>Nadir GH (ng/mL)</td>
<td>2 (2.1-3.8)</td>
<td>1.5 (0.8-4.5)</td>
<td>0.8</td>
</tr>
<tr>
<td>TSH (µU/mL)</td>
<td>1 (0.5-1.9)</td>
<td>1.2 (0.6-2.2)</td>
<td>0.77</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>1.1±0.4</td>
<td>1±0.3</td>
<td>0.43</td>
</tr>
<tr>
<td>FT3 (pg/mL)</td>
<td>2.6 (2-3.5)</td>
<td>2.9 (2.1-3.8)</td>
<td>0.85</td>
</tr>
<tr>
<td>Cortisol (µg/dL)</td>
<td>9.1 (7.3-12.8)</td>
<td>10.1 (6.4-14.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>Secondary Hypothyroidism</td>
<td>1 (%5)</td>
<td>8 (%10)</td>
<td>0.54</td>
</tr>
<tr>
<td>Secondary Hypoadrenalism</td>
<td>1 (%5)</td>
<td>6 (%7)</td>
<td>0.63</td>
</tr>
<tr>
<td>Secondary Hypogonadism</td>
<td>2 (%10.5)</td>
<td>17 (%20.5)</td>
<td>0.42</td>
</tr>
<tr>
<td>Residual adenoma</td>
<td>10 (%53)</td>
<td>47 (%57)</td>
<td>0.36</td>
</tr>
<tr>
<td>Disease remission</td>
<td>8 (%42)</td>
<td>31 (%37)</td>
<td>0.19</td>
</tr>
<tr>
<td>Remission at last control</td>
<td>12 (%63)</td>
<td>56 (%67.5)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

BMI: Body mass index, IGF-1: Insulin-like growth factor 1, GH: Growth hormone, TSH: Thyroid-stimulating hormone, FT4: Free thyroxine, FT3: Free triiodothyronine, ES: Empty sella

**Figures**

![Images](image1.png)
Figure 1

Coronal (a) and sagittal (b, c) images of contrast-enhanced pituitary magnetic resonance imaging (MRI) demonstrated a microadenoma (thick-arrows) localized to the right inferolateral part of the adenohypophysis, with less enhancement compared to the gland. Please note the “empty sella” appearance (thin-arrow) on the sagittal image (c). 1.5 Tesla MRI device (SIGNA Explorer, GE Medical Systems).

The pituitary magnetic resonance imaging of two patients with coexistence of acromegaly and primary empty sella

Figure 2

Coronal (a) and sagittal (b, c) contrast-enhanced pituitary magnetic resonance images of a 52-year-old female patient showed an adenoma (thick-arrows) invading the right cavernous sinus and a slight left displacement of the pituitary stalk (arrowhead). “Empty sella” appearance (thin-arrow) was observed on the parasagittal view from just lateral to the infundibular stalk as well. 1.5 Tesla MRI device (Intera, Philips).

The pituitary magnetic resonance imaging of two patients with coexistence of acromegaly and primary empty sella