Increased Incidence of Intracranial Meningiomas in Patients With Acromegaly

**BACKGROUND:** An increased incidence of various neoplasms has been described in patients with acromegaly, and there is evidence to suggest that growth factors are risk factors for the development of meningiomas.

**OBJECTIVE:** To study if patients with acromegaly are more at risk for developing intracranial meningiomas.

**METHODS:** We conducted an observational study on 221 consecutive acromegalic patients recruited between January 1, 2000 and December 31, 2015, and 357 consecutive patients with a nonsomatotropic pituitary adenoma recruited between March 1, 2015 and December 31, 2016, in our institution. Patients underwent a gadolinium-enhanced 3D T1 brain magnetic resonance imaging to look for meningiomas. The proportion of meningiomas was compared between the 2 groups, and the standardized incidence ratio (SIR) was computed from the incidence rates of meningiomas observed in the population of acromegalic patients and compared to that of the general population given by the local registry of central nervous system tumors.

**RESULTS:** Patients with acromegaly had a significant risk for developing intracranial meningiomas as compared to patients without acromegaly (7.7% vs 2.2%, \( P = .005 \), \( OR = 3.45 [1.46; 8.15] \)). There was a significant increased incidence of intracranial meningiomas in patients with acromegaly (SIR = 126 [25; 367]) as compared to the general population.

**CONCLUSION:** Our study suggests strongly that patients with acromegaly are more at risk for developing intracranial meningiomas.

**KEYWORDS:** Acromegaly, Growth hormone, Insulin-like growth factor 1, Incidence, Meningioma

**ABBREVIATIONS:** CI, confidence interval; CNS, central nervous system; GH, growth hormone; MRI, magnetic resonance imaging; SIR, standardized incidence ratio
of acromegalic patients with that of a control cohort of patients without acromegaly. Then, we compared the incidence of meningiomas in acromegalic patients with that of the local population based on the data of the local brain tumors registry.

METHODS

Patients

We studied a population of 221 consecutive patients who were diagnosed with acromegaly in our institution between January 1, 2000 and December 31, 2015. The diagnosis of acromegaly was made according to the published guideline of the Endocrine Society, which included increased IGF-1 levels associated with nonsuppressible plasma GH following a glucose tolerance test. All of the patients had a pituitary adenoma diagnosed by pituitary magnetic resonance imaging (MRI). All cases with a questionable diagnosis were reviewed by a senior endocrinologist.

In parallel, we prospectively analyzed a cohort of 357 patients with a nonsomatotropic pituitary adenoma consecutively explored in the Endocrine Imaging Department of our institution between March 1, 2015 and December 31, 2016 (control cohort). Hormonal investigation included at least the measurement of plasma IGF-1, prolactin, FT4 and TSH, testosterone or estradiol with plasma gonadotrophins, and cortisol, and complementary/dynamic investigations of the pituitary function when needed. The initial investigations and follow-up were also performed in the same endocrinology department of our institution and all cases with a questionable diagnosis were reviewed by a senior endocrinologist.

Patient Consent

This work was performed in compliance with the Declaration of Helsinki. The regional ethics committee was informed about this study and did not deem it necessary to compile an official report, because it did not modify current patient care or require the use of further radiological examination. Consent was, however, obtained from patients (or their family) for the examination of their medical records and brain imaging. All patients were over 18 yr old.

Clinical Information

Sex, age at adenoma diagnosis, age at the time of the first brain imaging, age at meningioma diagnosis, history of malignant diseases, and previous encephalic radiotherapy were collected for all patients. Because meningiomas are part of the MEN1 syndrome, the presence of MEN1 was clinically ruled out in all patients by a senior endocrinologist. In addition, DNA sequencing of the MEN1 gene was performed in patients who had been diagnosed with pituitary adenoma before the age of 30.

Local Registry of CNS Tumors

Beginning in May 1999, all patients in whom any new primary tumor of the CNS, including meningioma, has been diagnosed, whether symptomatic or asymptomatic, were prospectively registered. Pituitary tumors, tumors associated with AIDS, recurrence of tumors, and metastatic tumors were excluded. The following parameters were systematically recorded: date of birth, sex, postal code of residence, date of diagnosis, topography, and tumor histological type and grade. Overall, age- (5-yr age intervals), and sex-specific crude incidence rates were calculated and expressed per 100 000 per year.

Brain Imaging

The patients included in this study underwent a 1.5 or 3 Tesla MRI including a gadolinium-enhanced 3D gradient-echo T1 sequence (TR 9 msec, TE 4 msec, and 1-mm isovoxel). All the images were reviewed separately by 2 neurosurgeons and a senior neuroradiologist in a blinded fashion.

Calculation of Incidence Ratios

Standardized incidence ratios (SIRs) were computed in the cohort of patients with acromegaly to compare the incidence of meningioma with that in the general population. The SIR was calculated as the ratio of the number of meningiomas observed in the study population divided by the number of meningiomas expected if this population had the same age, gender, and calendar year-specific rates as the general population. CI of 95% for SIR were calculated with Breslow’s formula. The expected number of meningiomas was calculated from the local registry of primary CNS tumors in 2013. In order to minimize measurement bias, the observation period was restricted to the period between January 1, 2015 and December 31, 2016, when meningiomas were prospectively checked.

Statistical Analysis

Quantitative variables were presented as mean with standard deviation or as median with interquartile range accordingly with their distribution and were compared using the Student’s test. Qualitative variables were compared using Fisher’s exact test or the X² test according to the number of observations and adjusted with the Mantel-Haenszel test for confounding factors for comparison between demographic characteristics and meningioma proportion between the 2 cohorts. Multivariate analysis for comparison between acromegalic patients with and without meningiomas was performed with logistic regression with the Firth’s penalized likelihood method as a correction because standard logistic regression may generate biased estimation when the number of events are small. Differences were considered to be statistically significant if P < .05. SPSS Statistics software was used.

RESULTS

Study Population

Demographic characteristics were unbalanced between cohorts for sex ratio, with significantly more women in the acromegaly cohort. There was no difference between groups for the age at brain imaging, the duration of imaging follow-up, a history of other cancers, a MEN-1, or prior pituitary radiotherapy (Table 1).

Of the 357 patients with a nonsomatotropic pituitary adenoma, 49% of patients had a nonfunctioning adenoma, 33% had a prolactinoma, 17% had Cushing disease, and 1% had a thyrotroph adenoma.

Among the 221 acromegalic patients, 195 underwent a gadolinium-enhanced whole-brain MRI. The other 26 (11.7%) patients were lost to follow-up and were considered to have no meningioma for the analysis. In the other cohort, all of the 357 patients underwent a gadolinium-enhanced whole-brain MRI.

In the acromegaly group (221 patients), 21 meningiomas were identified in 17 distinct individuals (7.7%), as 1 patient presented

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with 4 tumors (treated for prostate cancer by cyproterone acetate). Of the 357 patients with a nonsomatotropic pituitary adenoma, 8 meningiomas were diagnosed in 8 distinct patients (2.2%), \( P = .003, \ OR = 3.6 \ [1.54; 8.57] \) (Table 1). Furthermore, after adjusting for gender, the difference between groups for meningioma proportion remained statistically significant (\( P = .005, \ OR = 3.45 \ [1.46; 8.15] \)).

Characteristics of Patients with Meningiomas

Demographic and clinical characteristics of patients with a meningioma (Table 2) showed that there was no significant difference between the 2 groups in age at meningioma diagnosis, sex ratio, history of MEN-1, and previous encephalic radiotherapy, which are the well-known potential confounding factors when studying meningiomas occurrence in a population.

Meningiomas were no different between groups with regard to the mean size, the clinical relevance (Figures 1 and 2), and the localization (Table 3). Of the 21 meningiomas in acromegalic patients, 2 required surgical intervention: one located in the foramen magnum, which was symptomatic (swallowing disorders and tetrapyraldal syndrome) and one frontal meningioma, which was responsible for dysexecutive troubles (WHO grade I in both cases).

The timing of the occurrence of meningiomas in relation to the diagnosis of acromegaly could not be confirmed in 8 cases, because the first MRI done for the diagnosis of the pituitary adenoma did not cover the whole brain (NA, not available; Table 3). In 11 cases, the meningiomas were already visible on the first MRI done for the diagnosis of the pituitary adenoma (synchronous cases). In 2 cases, the meningiomas appeared, respectively, 3 and 11 yr after the diagnosis of the acromegaly (metachronous cases). For the first patient, acromegaly was not controlled despite of treatment by somatostatin analogs, pituitary surgery, GH-receptor antagonist, and dopaminergic analogs. IGF-1 was at 238 ng/mL (1.2 N) at meningioma diagnosis. For the second patient, acromegaly was not controlled despite of treatment by somatostatin analogs, 2 pituitary surgeries, and dopaminergic analogs. IGF-1 was at 247 ng/mL (1.2 N) at meningioma diagnosis.

The timing of the occurrence of meningioma in relation to the diagnosis of nonsomatotropic pituitary adenoma could not be confirmed in 4 cases (NA). In 3 cases, the meningiomas were already visible on the first MRI done for the diagnosis of the pituitary adenoma (synchronous cases). In one case, the meningiomas appeared during the follow-up after the diagnosis of the adenoma (metachronous).

When comparing acromegalic patients with or without meningiomas, we observed that patients with a MEN-1 were more at risk for a meningioma (11.7% vs .5% \( P = .003 \)) (Table 4).

SIR of Meningioma

The flow chart (Figure 3) describes the selection of the patients with acromegaly to estimate the SIR for meningioma incidence over the period 2015 to 2016. Of the 221 acromegalic patients, 111 patients were included in the SIR calculation.

For the 2-yr study period, we observed 3 meningiomas in 111 acromegalic patients (188 person-years) vs .024 meningiomas expected. The estimated SIR (95% CI) for meningioma incidence was 3/0.024 = 126 [25; 365].

DISCUSSION

We found that patients with acromegaly had a significantly increased risk for harboring intracranial meningioma as compared to patients without acromegaly (7.7% vs 2.2%, \( P = .005, \ OR = 3.45 \ [1.46; 8.15] \)). Furthermore, we found that there was a significant increased incidence of intracranial meningiomas in patients with acromegaly as compared to the general population (SIR = 126 [25; 367]). These results strengthen the hypothesis of an association between acromegaly and intracranial meningioma, as previously suggested by case reports (Table 5).
Studying the incidence of meningioma, a relatively rare disease (average annual incidence rate around 6.5/100,000 inhabitants between 2000 and 2011), in a population with a rare disease (acromegaly) is challenging. The strengths of our study are the large cohort of patients with acromegaly and the comparison of the incidence rates to a well-structured local brain tumor registry. Furthermore, we showed that patients with acromegaly were more at risk for having meningiomas in 2 ways. First, we made a comparison between 2 cohorts. However, this method may be biased because of the definition of the control group that is a selected population for a specific condition (ie, a pituitary adenoma). Furthermore, the control group was a much recent cohort compared to the acromegalic cohort. However, we do not think that it may play a significant role in the study. Indeed, there were no major changes in both surgical and medical treatments of all kinds of pituitary adenomas between the 2000 to 2015 and 2015 to 2016 time periods. The main change was the introduction of the long-acting analogs in acromegaly in the years 2000. Overall, as it has been shown that the comparison between cohorts might lead to an overestimation of the risk of tumors in previous studies, we performed a second analysis by calculating the SIR of meningiomas between patients with acromegaly and the general population based on the data of the local Registry of CNS tumors.

Our results showed a statistical association between 2 pathologies: acromegaly and intracranial meningioma. However, we could not go further in the demonstration of the association of acromegaly with the development of meningiomas. It was very difficult to study the onset of meningiomas with respect to the beginning of acromegaly. Indeed, acromegaly is a disease in which symptoms develop insidiously over decades, often resulting in a delay of 7 to 10 yr in diagnosis after the estimated onset of symptoms. The onset of development of a given meningioma is quite impossible to establish, as these tumors present several growth patterns. We could show that a meningioma developed after the onset of acromegaly in only 2 cases, and this situation was reported in 5 cases in the literature (Table 5).

It would have been essential to know the GH and IGF-1 blood levels and to establish how the disease was controlled at the onset of the meningioma. This would have made it possible to correlate these variables with the growth pattern of the tumor. However, the difficulty in precisely dating the onset of meningioma relative to the course of acromegaly made it impossible to assess the hormonal mechanisms of meningioma development. We still could record these data for the metachronous cases. Interestingly, in these cases, acromegaly was uncontrolled at the time of meningioma occurrence.

Moreover, the cumulative exposure to high GH and IGF-1 levels over a long period of time (theoretically corresponding to the time between the onset and the control of the acromegaly, which cannot be established) and may be more relevant for studying tumor initiation and growth than the levels at a single point in time. This probably explains why strong evidence linking elevated GH and IGF-1 with increased cancer rates is lacking in the literature.

Many studies focused on the cancer risk in patients with acromegaly with controversial results. Cancer classically associated with acromegaly is the colorectal cancer, and therefore, colonoscopy screening is recommended. Other cancers include thyroid, breast, prostate, and lung. Although cancer incidence varies widely amongst studies, it appears to be consistently elevated mainly in patients with uncontrolled disease. Indeed,
FIGURE 2. Sagittal T1 nonenhanced MRI reveals incidental parietal dural-based lesion A in an acromegalic patient. The Coronal T2 MRI reveals a macroadenoma invading the sphenoid sinus B. The adenoma was treated with somatostatin analog and surgery with a good response C (coronal T2 imaging), whereas the meningioma was noted to progress in size on follow-up sagittal contrast enhanced MRI D.

TABLE 3. Characteristics of Meningiomas in Acromegaly and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>Acromegaly</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (meningiomas)</td>
<td>21</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Occurrence in relation to the adenoma diagnosis</td>
<td></td>
<td></td>
<td>.77</td>
</tr>
<tr>
<td>N/A</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Synchronous</td>
<td>11</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Metachronous</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Symptomatic meningioma</td>
<td>2 (9.5%)²</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Mean size (mm)</td>
<td>12.5 ± 8.5</td>
<td>14.1 ± 8.2</td>
<td>.64</td>
</tr>
<tr>
<td>Localization</td>
<td></td>
<td></td>
<td>.16</td>
</tr>
<tr>
<td>Anterior convexity¹</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Posterior convexity¹</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Anterior and middle fossa</td>
<td>11</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Posterior fossa</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Falc cerebri</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cerebellar tentorium</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
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</table>

¹Anterior/posterior convexity defined with regards to the coronal suture.
²One was symptomatic at diagnosis; one became symptomatic during follow-up.

recent studies conducted on large number of patients have shown an increase in the proportion of deaths due to cancers in patients with acromegaly during the last decades.²⁴ In Vitro, animal studies and studies in nonacromegalic cancer patients have established a role for the GH/IGF-1 axis in tumor progression and possibly initiation,²⁵ but data in acromegalic patients are less convincing.²³

Our study showed a significant association between acromegaly and the incidence of meningiomas but did not establish a causal relationship. However, the role of GH and IGF-1 is strongly supported by in Vitro and animal studies. Indeed, overexpression of the GH and the IGF-1 receptors (IGF-1r) has been described for meningiomas.⁷,⁸,²⁶ Friend et al⁸ showed that the blockage of the GH receptor by a specific antagonist decreased DNA synthesis in meningioma cells from 20% on average. McCutcheon et al⁹ showed a decrease in the mean tumor volume (xenografted WHO grade I meningioma) after 8 wk of pegvisomant injections in mice. It was also shown that meningioma cell proliferation is mediated by IGF-1⁸ and that blocking IGF-1 with fenretinide inhibited this effect, especially by blocking the Akt/mTOR pathway.⁷

The PI3K/Akt/mTOR pathway is one of the major pathways involved in meningioma oncogenesis. This pathway seems to be overactivated, especially by the loss of function of Merlin, which is a negative regulator of mTOR. Merlin is a protein encoded by the
NF2 gene, which expression is inactivated by the loss of heterozygosity on the chromosome 22q, which is one of the most common cytogenetic alterations in meningiomas.\(^2\) It is well known that meningiomas express somatostatin receptors, especially SST2,\(^2\) and it has been shown that activation of SST2 by analogs decreased the activity of the PI3K/Akt pathway.\(^2\) These observations are of importance for 2 reasons. First, most acromegalic patients in our study were treated by somatostatin analogs before and after pituitary surgery. This could have interfered with the natural history of meningiomas in this cohort. Secondly, medical treatment options for meningiomas are developed in light of these data, especially by combining everolimus (a mTOR inhibitor) and somatostatin analogs (octreotide and more recently pasireotide) based on the potentially synergistic effect of these 2 molecules.\(^2\),\(^3\)

Clinically, the effects of GH administration on meningioma development have been studied with controversial conclusions,\(^3\)\(^-\)\(^4\) because of the various indications of GH administration (GH deficit supply or not) and the frequency of encephalic radiotherapy in the histories of the patients, which is one of the main confounding factor when studying meningiomas.\(^3\)\(^5\) In light of these findings, the potential effect of pegvisomant (GH receptor antagonist) on meningioma growth could, therefore, be clinically studied, although Drake et al\(^1\) reported the case of a 74-yr-old acromegalic woman with a meningioma who was treated with pegvisomant without a discernible inhibitory effect on meningioma growth.

Aside from the potential role of GHs on meningioma development, we observed in our study that acromegalic patients with a MEN-1 were significantly more at risk for a meningioma (11.7% vs .7%, \(P = .006\)). However, when suppressing patients with a MEN-1 from the analysis, the difference between groups for meningioma proportion was still significant (\(P = .007\), data not shown). These data suggest that MEN-1 was not sufficient for explaining the highest risk of having a meningioma in the acromegaly group, but that this condition might potentiate the association between acromegaly and meningioma. This is in accordance with the findings of Asgharian,\(^1\) who showed that

\[\text{TABLE 4. Comparison Between Acromegalic Patients With or Without Meningioma}\]

<table>
<thead>
<tr>
<th>Meningioma</th>
<th>No meningioma</th>
<th>(P)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>17</td>
<td>204</td>
</tr>
<tr>
<td>Age at first brain imaging (years)</td>
<td>59.3 ± 11.8</td>
<td>53.2 ± 15.2</td>
</tr>
<tr>
<td>Sex ratio M/F</td>
<td>.54</td>
<td>.67</td>
</tr>
<tr>
<td>MEN-1</td>
<td>2 (11.7%)</td>
<td>1 (.5%)</td>
</tr>
<tr>
<td>Other cancer</td>
<td>6 (35%)</td>
<td>27 (13%)</td>
</tr>
<tr>
<td>Previous radiotherapy</td>
<td>0 (0%)(^1)</td>
<td>28 (13.7%)</td>
</tr>
</tbody>
</table>

\(^1\)One patient had a meningioma diagnosed on October 27, 2011, and underwent pituitary radiotherapy beginning in April 2012.
\(^2\)Logistic regression with Firth’s penalized likelihood method.
patients with neuroendocrine pancreatic tumors in the context of MEN-1 were more at risk for developing meningiomas.

Finally, the implications of this study affect acromegalic patients. Indeed, a brain MRI screening to check for meningiomas could be recommended, at the initial diagnosis and every 3 or 5 yr, and even more in the context of a MEN-1. Furthermore, regular follow-up of these tumors would be interesting in order to correlate their growth pattern with acromegaly control under treatment.

Limitations

One limitation of our study is the comparison between 2 nonmatched cohorts with significantly more women in the acromegaly group. However, when adjusting the analysis for the sex ratio, we still found a significant difference in meningioma proportion between groups ($P = .005$). Furthermore, we did not find any difference in sex ratio among patients with a meningioma from the acromegaly and the control cohorts. Another limitation is the number of acromegalic patients who did not have a brain MRI (26, 11.7%), which might underestimate our results as we considered these patients not to have a meningioma. There are also some limitations in calculating the SIR. First, as the registry includes only patients from a specific area, we excluded from analysis all the acromegalic patients who lived outside this area. Second, to limit measure bias, we restricted the observation period between January 1, 2015 and December 31, 2016, which allowed for a prospective observation of meningiomas. These methodological restrictions led to a smaller population of acromegalic patients observed during a short time (188 person-years) explaining the large 95% CI. Furthermore, by comparing a population specifically checked for meningiomas with 3D T1 enhanced MRI to the data of a population-based registry, we induced a measurement bias because the general population is not systematically checked for meningiomas, unlike the acromegalic patients of this study. This might have led to an overestimation of the incidence ratio.

CONCLUSION

We have added evidence with limitations that increases the concern that patients with acromegaly may have an increased incidence of meningioma. A larger scale replication study with fewer limitations is required for a firm conclusion. Based on experimental data, we can hypothesize that this association might be partially mediated by the effects of GH and IGF-1 on tumor initiation and growth. According to our data, the context of a MEN-1 potentiates the risk of developing a meningioma in patients with acromegaly. Meanwhile, and from a clinical perspective, our study suggest to carefully screening patients with acromegaly for meningiomas at the initial diagnosis and at regular intervals.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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