Somatomedin C/Insulin-like Growth Factor I Levels After Treatment of Acromegaly*

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ABSTRACT

An in-house method was used, including dissociation of Somatomedin C/insulin-like Growth Factor I (Sm-C/IGF-I) binding proteins with acid and extraction of Sm-C/IGF-I by C-2 cartridge before radioimmunoassay, to measure plasma Sm-C/IGF-I levels in three groups of patients — total of 19 — with acromegaly who underwent transsphenoidal removal of pituitary tumors. In group A (n = 7), the Sm-C/IGF-I levels did not decrease to normal on postoperative day 1 even though the growth hormone concentration had decreased to normal. In group B (n = 4), the Sm-C/IGF-I level decreased to normal in three of the four patients on postoperative day 4, but it remained elevated in one. At two months postoperatively, all four patients had normal values. Group C patients (n = 8) had had an operation two to 23 years previously, and all remained in remission with normal Sm-C/IGF-I levels. Our findings indicate that the Sm-C/IGF-I assay is useful for monitoring acromegaly after transsphenoidal removal of pituitary tumors, but it should be ordered at least four days postoperatively.

Introduction

Somatomedin C, also called insulin-like growth factor I (Sm-C/IGF-I), has proved to be an excellent tumor marker for growth hormone (GH)-producing pituitary adenomas because plasma levels in patients with acromegaly do not overlap with levels in normal subjects.² However, after treatment of acromegaly, a poor correlation of the plasma Sm-C/IGF-I concentration with the GH level and clinical response has been reported.⁸ These observations suggest that Sm-C/IGF-I is an excellent tumor marker for the diagnosis of acromegaly but a poor marker in follow-up after treatment of the disease. Alternatively, a good correlation between Sm-C/IGF-I levels and clinical response has been reported by other
investigators. In an attempt to resolve this controversy, our in-house extraction method of Sm-C/IGF-I radioimmunoassay (RIA) was used to study retrospectively the circulating levels of Sm-C/IGF-I in patients with acromegaly who had transsphenoidal removal of pituitary tumors.

Methods

Measurement of Sm-C and GH

Somatomedin-C was measured by an in-house radioimmunoassay (RIA) after removal of Sm-C/IGF-I binding proteins from plasma. The detailed procedure was published previously in this journal. In brief, Sm-C/IGF-I was dissociated from its plasma-binding proteins with 1 M acetic acid and then extracted with a C-2 cartridge. The Sm-C/IGF-I extracted on the cartridge was eluted, dried, reconstituted, and measured by RIA with an antiserum from a goat immunized with whole molecules of synthetic Sm-C/IGF-I. The synthetic Sm-C/IGF-I was also used to prepare tracer (125I-labeled Sm-C/IGF-I) and standard. Free and bound fractions were separated with a donkey anti-goat immunoglobulin. The normal range of Sm-C/IGF-I is age- and sex-dependent: for adults older than 20 years, it is less than 16.0 nmol per L.

A fasting morning GH specimen was collected and analyzed by RIA. The normal value for males is 0.23 nmol per L (5 ng per mL) or less, and for females it is 0.46 nmol per L (10 ng per mL) or less.

Intra-assay and interassay coefficients of variation for the Sm-C/IGF-I assay were both 10 percent. Intra-assay and interassay coefficients of variation for the GH assay were 10 percent and 11 percent, respectively.

Subjects and Specimens

This was a retrospective study; all specimens were obtained when Sm-C/IGF-I and GH tests were ordered. For the GH assay, serum specimens were used. For the Sm-C/IGF-I assay, blood was drawn in ethylenediamine tetra-acetic acid (EDTA) tubes and centrifuged immediately to remove blood cells. The plasma was frozen at −70°C until assayed.

Nineteen adult patients (nine male and 10 female) who had acromegaly after transsphenoidal removal of pituitary tumor were divided into three groups. Group A consisted of seven patients (four male and three female) in whom Sm-C/IGF-I was measured preoperatively and again one day postoperatively. Group B consisted of four patients (one male and three female) in whom Sm-C/IGF-I was measured preoperatively, one day and four days postoperatively, and two months, one year, and two years postoperatively when the patients returned for follow-up. Group C consisted of eight patients (four male and four female) who had their Sm-C/IGF-I levels determined two to 23 years after removal of the pituitary tumor and were still in remission.

Results

Sm-C/IGF-I and GH Concentrations Before and After Operation

In group A (seven patients), the Sm-C/IGF-I levels were elevated preoperatively and one day after removal of pituitary tumor, even though the serum GH values had immediately returned to normal or very close to normal levels (table I).

In group B (four patients), Sm-C/IGF-I levels all were elevated preoperatively and on postoperative day one (table II), similar to group A. On postoperative day four, the Sm-C/IGF-I values in one patient still had not returned to normal, but they were normal in the other three. At two months postoperatively, Sm-C/IGF-I concentrations were normal in all the patients and remained normal at one year postoperatively. Two of the four
Somatomedin-C/insulin-like growth factor-I (Sm-C/IGF-I) and growth hormone levels preoperatively and 1 day after removal of pituitary tumor for acromegaly in Group A

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Sm-C/IGF-I, nmol/L a</th>
<th>GH, nmol/L b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop</td>
<td>Postop</td>
</tr>
<tr>
<td>39 y/M</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>54 y/F</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>30 y/F</td>
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<td>52</td>
</tr>
<tr>
<td>39 y/F</td>
<td>63</td>
<td>55</td>
</tr>
</tbody>
</table>

a Normal, < 16 nmol/L.
b Normal, ≤ 0.23 nmol/L in males and ≤ 0.46 nmol/L in females.

Patients followed to two years postoperatively still had normal Sm-C/IGF-I levels. The GH values were all elevated preoperatively but were normal from postoperative day 1 on (data are not shown in table II).

In group C, Sm-C/IGF-I levels were normal in all eight patients still in remission two to 23 years after operation (table III).

Discussion

In this retrospective study, three groups of acromegalic patients who had successful transsphenoidal removal of a pituitary tumor were used to illustrate that Sm-C/IGF-I levels will not return to normal immediately after operation but will return to normal by two months and will remain normal for up to 23 years.

The data from all three groups indicate that postoperative Sm-C/IGF-I levels in acromegalic patients will return to normal. However, they require a longer time to become normal than does GH. Growth hormone returns to normal by the first day after operation. The Sm-C/IGF-I levels were elevated on postoperative day one in all the patients. On postoperative day four, one patient still had an elevated Sm-C/IGF-I value; however, Sm-C/IGF-I concentrations stayed within the normal range throughout remission from two months to 23 years.

Determining the Sm-C/IGF-I concentration on postoperative day one is unnecessary. In our study, none of the patients had normal Sm-C/IGF-I values on day one after operation. Their levels were similar to the preoperative levels. On postoperative day four, use of the Sm-C/IGF-I test to monitor the success of the operation will still be of limited usefulness, as demonstrated by the elevated value in one of the four patients in group B. The Sm-C/IGF-I test is worthwhile at two months postoperatively. From two

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Sm-C/IGF-I, nmol/L a</th>
<th># Years Postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>61 y/M</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>46 y/M</td>
<td>12</td>
<td>2</td>
</tr>
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<td>65 y/M</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>35 y/F</td>
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<tr>
<td>28 y/F</td>
<td>15</td>
<td>7</td>
</tr>
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<td>7</td>
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</tr>
<tr>
<td>68 y/F</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>62 y/M</td>
<td>6</td>
<td>23</td>
</tr>
</tbody>
</table>

a Normal, < 16 nmol/L.
months to 23 years after operation, all the patients remained in remission with Sm-C/IGF-I values within the normal range.

All blood-circulating Sm-C/IGF-I is protein-bound.\textsuperscript{1,5,9,10,11} The delay of Sm-C/IGF-I to return to normal was most likely caused by binding proteins, which have a longer half-life than that of unbound Sm-C/IGF-I.\textsuperscript{3,4} Currently, there is no reliable and practical method available to clinical laboratories to determine these binding proteins. However, removal of the interference of binding protein from blood specimens is not difficult.

Our findings corroborate the findings of Roelfsema et al\textsuperscript{7} that Sm-C/IGF-I is a useful clinical marker in the treatment of acromegaly. In the laboratory of Roelfsema and colleagues, hydrochloric acid was used to dissociate binding protein, and C-18 cartridge was used to purify Sm-C/IGF-I. The Sm-C/IGF-I was then measured with a commercially available RIA kit that included antibodies directed to a fragment of Sm-C/IGF-I in the amino acid sequence of 53 to 70. Their method is similar to ours in that both of us used acid dissociation and cartridge extraction before RIA measurement of Sm-C/IGF-I, even though our work used different acid, cartridges, and RIA methods (acetic acid, C-2 cartridge, and RIA directed to whole molecules of synthetic Sm-C/IGF-I instead of to a fragment of Sm-C/IGF-I). The fact that our findings were similar to theirs suggests that removal of binding proteins by diverse methods gives similar results.

Both of our findings had discrepancies with those of another group of investigators\textsuperscript{8} who sent their specimens to a commercial laboratory that used a direct assay without removal of binding proteins before RIA measurement of Sm-C/IGF-I.\textsuperscript{3,4} The discrepancy in postoperative Sm-C/IGF-I levels appeared to be due to the interference of binding protein in their RIA measuring system. The removal of binding proteins before RIA measurement probably is necessary to prevent such interference. In March 1991, the same commercial laboratory also added a test of extraction Sm-C/IGF-I RIA.

The slower decrease in the Sm-C/IGF-I level than in the GH value may suggest that the GH test can be used to monitor current pituitary gland secretion and the Sm-C/IGF-I test can be used to monitor previous GH secretion of a few days earlier. This pair of tests for monitoring GH and Sm-C/IGF-I in patients with acromegaly is similar to the pair of tests for monitoring glucose and glycohemoglobin in patients with diabetes mellitus.

In conclusion, our study indicates that the Sm-C/IGF-I assay is useful for monitoring acromegaly after transsphenoidal removal of pituitary tumor. The removal of binding protein before RIA may be necessary. The level of Sm-C/IGF-I may not return to normal before postoperative day four. However, two months after operation, Sm-C/IGF-I levels should all have returned to normal, and the hormone levels should remain normal throughout the remission period.

References


