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Case study

Has acromegaly been diagnosed earlier?

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ABSTRACT

Purpose: We investigated whether acromegaly has been diagnosed earlier at the Niigata Medical and Dental University Hospital.
Methods: Patients with acromegaly (n = 81) who underwent their first transsphenoidal surgery from 2006 to 2015 were reviewed. Two groups were compared: those who underwent surgery between 2006 and 2010 (n = 35) and those who underwent surgery between 2011 and 2015 (n = 46). We compared clinical features and serum levels of the growth hormone (GH) and insulin-like growth factor-1 (IGF-1), hypertension (HT) and diabetes mellitus (DM) prevalence between the two groups.
Results: Compared with the early group, microadenomas (<10 mm) were more prevalent in the late group (0% vs. 15.2%, $p < .05$). Serum IGF-1 standard deviation score (SDS) was significantly lower in the late group (8.57 ± 2.50 vs. 6.44 ± 2.30, $p < .001$). In both groups, mean IGF-1 SDS was significantly lower in patients without DM than in those with DM (6.9 ± 2.6 vs. 8.3 ± 2.4, $p = .02$). Logistic regression analysis showed that serum GH and IGF-1 levels were significantly higher in patients with DM than in those without DM.
Conclusion: Regarding operated cases of GH-producing pituitary adenoma, acromegaly clinical manifestations tended to be milder at diagnosis in later years of the decade, and acromegaly was diagnosed at lower IGF-1 levels and in smaller lesions. Further study is mandatory for the generalization of this trend.

1. Introduction

Acromegaly is often complicated by HT, DM, or other comorbidities. Patients with acromegaly have a reduced life expectancy because of cardiovascular, cerebrovascular, and respiratory diseases [1]. Tumor size increases insidiously until typical features develop, at which time it may be quite large [2].

Transsphenoidal surgery is indicated as the first-line therapy [3,4]. The biochemical remission rate following surgery performed by an experienced surgeon is around 70% [5]. Favorable postoperative outcomes are likelier with a smaller tumor, lower Knosp grade, and lower preoperative GH and IGF-1 levels [6]. Patients with incomplete cure require medications and/or radiation therapy [3,7,8]. Better surgical results and subsequent patient outcomes can be expected if GH-secreting pituitary adenomas are detected earlier in the course of the disease. However, there are very few data available to determine whether these tumors are increasingly being detected at an earlier stage.

The Niigata Prefecture of Japan has a population of approximately 2.3 million. Most residents of this prefecture with pituitary tumors are treated surgically at the Department of Neurosurgery, Niigata University Medical and Dental Hospital. Recently, we noticed that our patients with acromegaly tended to have milder clinical features compared with those presenting in earlier years [9]. Thus, we investigated changes in the clinical characteristics of patients with acromegaly between the early and late years of the past decade. This study is intended to clarify the trends in disease detection and to determine the clinical significance of the results.

2. Subjects and methods

2.1. Patients

From 2006 to 2015, 81 patients with acromegaly (32 men and 49 women) underwent transnasal endoscopic surgery at the

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Niigata University Medical & Dental Hospital. All patients provided written informed consent.

Various specialty physicians suspected the diagnosis: internal medicine (25 patients), neurosurgery (18), neurology (6), otorhinolaryngology (6), orthopedic surgery (4), general surgery (3), cardiology (3), dentistry (3), gynecology (2), anesthesiology (1), cardiovascular surgery (1), ophthalmology (1), psychiatry (1) and unknown (1). Six cases were diagnosed during a regular health examination.

From patient charts, clinical and hormonal data were retrospectively collected, which included presenting complaints, symptom durations, basal serum GH and IGF-1 levels at diagnosis, comorbidities, and postoperative course. Radiological findings were recorded including the pituitary tumors size and heel-pad thickness at diagnosis.

The time from the appearance of initial symptoms (nose, hands, or feet enlargement in most cases) noted until the diagnosis of acromegaly was based on interview.

Patients under treatment for either or both conditions at the time of acromegaly diagnosis and those with untreated diabetes (DM) and/or hypertension (HT), but who met the diagnostic criteria [10,11], were considered as having DM and/or HT.

2.2. Measurements

Serum GH levels were measured by an immuno-enzymometric assay (Tosoh Corporation, Tokyo, Japan) using a uniform recombinant human GH standard [7,12]. Reference values of GH were <0.64 ng/ml in males and 0.11–3.90 ng/ml in females.

Serum IGF-1 levels were measured by an immunoradiometric assay (Daiichi, Fujifilm RI Pharma Co., Ltd., Tokyo, Japan). Isojima et al. established age- and gender-specific IGF-I reference values for Japanese population [12], based on which serum IGF-1 levels were converted to IGF-1 SDS.

2.3. Statistical analysis

Two groups of patients were compared: those who underwent surgery between 2006 and 2010 (n = 35) and those who underwent surgery between 2011 and 2015 (n = 46).

We compared clinical features and serum GH and IGF-1 levels between the two groups. Where indicated, data are represented as mean ± standard deviation (SD) and were statistically compared using a *t*-test, and categorical variables are reported as percentages and compared using Fisher's exact test. Correlation between serum IGF-1 values and the operation period was examined using linear approximation.

To assess the association between serum GH and IGF-1 values at diagnosis and clinical features in patients, we examined differences between GH and IGF-1 levels and DM or HT status using a *t*-test. Odds ratio with 95% confidence intervals for DM and HT risk were calculated for several variables (age, sex, GH levels, IGF-1 levels, and SDS) by univariate logistic regression analysis using SPSS ver. 22.0 for Windows (SPSS Inc., Chicago, Illinois). $P < .05$ was considered statistically significant.

One woman in the early group with a >+17 SD baseline GH value (using GH value as an outlier) and one aged >75 years in the late group whose IGF-1 SDS could not be calculated were excluded from our statistical analyses.

3. Results

3.1. Differences in clinical characteristics

As shown in Table 1, sex, age at diagnosis, and time from symptom onset to diagnosis did not differ between the two groups. However, fewer cases were diagnosed in men <40 years in the early period (1/12, 8.3%) than in the late (8/20, 40%).

Patients with a <5 ng/ml serum GH value were seen more frequently in the late period (11.4% vs. 26.1%). No significant difference was seen in the ratio of patients with <22 mm heel-pad thickness for the two groups ($p = .204$), but in the linear approximation, heel- pad thickness and operation date showed a weak negatively correlation ($r = -0.29$, $p = .013$) (Fig. 1).

Although DM or HT prevalence was lower in the late group than in the early group, the difference was insignificant (DM: 38.2% vs. 28.3%; HT: 37.1% vs. 30.4%).

Microadenomas were found in seven patients in the late group. This difference was significant ($p = .037$).

Patients incidentally diagnosed with pituitary adenoma by MRI were more frequent in the late group (14.7% vs. 30.4%). Presenting complaints unrelated to GH-producing adenoma (e.g., health examination, trauma, common cold, spinal cord disease, forgetfulness, suicide attempt, Bell's palsy, and so on) were also more frequent in the late group (26.5% vs. 45.7%), although the difference was insignificant.

Eight of the 46 patients (17.4%) in the late group received additional postoperative treatment (cabergoline, 7; cabergoline + lanreotide + radiation, 1) as did nine of the 35 patients (28.5%) in the early group (cabergoline, 2; gamma knife, 3; octreotide, 1; bromocriptine, 4, with some overlap).

Postoperative normalization of age-related IGF-1 levels (within + 2 SD) and suppression of serum GH < 1.0 ng/ml after a 75-g OGTT or a random GH < 1.0 ng/ml occurred in 72.8% of the total sample,

Table 1
Clinical characteristics of patients with acromegaly diagnosed early or late in the decade 2006–2015.

	Early (2006–2010)	Late (2011–2015)	p-value
Number of patients and sex	35 (female, 23; male, 12)	46 (female, 26; male, 20)	.493
Age at diagnosis (years, mean)	52.7 (female, 53.1; male, 51.9)	50.7 (female, 54.5; male, 45.6)	.492
Time to diagnosis (years, mean)	9.03 ± 5.43	10.57 ± 6.33	.397
GH < 5.0 ng/ml	11.4% (4/35)	26.1% (12/46)	.158
Heel-pad thickness <22.0 mm	23.3% (7/30)	39.0% (16/41)	.204
Diabetes mellitus	38.2% (13/34)	28.3% (13/46)	.469
Hypertension	37.1% (13/35)	30.4% (14/46)	.635
Microadenoma (<10 mm in diameter)	0.0% (0/32)	15.2% (7/46)	**.037**
Detected incidentally	14.7% (5/34)	30.4% (14/46)	.119
Main complaint unrelated to adenoma	26.5% (9/34)	45.7% (21/46)	.104
Additional therapy after surgery	28.5% (9/34)	17.4% (8/46)	.416
Surgical remission rate with 75 g OGTT nadir <1.0 ng/ml	74.2% (26/35)	71.7% (33/46)	>.999
Diabetic-pattern at postoperative 75 g OGTT	22.9% (8/35)	17.4% (8/46)	.583

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