Presurgical treatment with somatostatin analogues in growth hormone-secreting pituitary adenomas: A long-term single-center experience

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ABSTRACT

Objective: Acromegalic patients with macro- or giant adenomas often had poor prognosis after surgery. Somatostatin analogues (SSAs) show high effectiveness in both tumor shrinkage and serum GH reduction. But the role of SSAs in pre-surgical treatment and the management among macro- and giant adenomas remains controversial.

Patients and Methods: A total of 100 acromegalic patients with macro- or giant adenomas that underwent surgery in our institution between January 2010 and December 2016 were enrolled in the current retrospective study. The relationships between several potential parameters and surgical outcomes were further analyzed.

Results: The overall long-term remission rate was 45% accompanied by gross total resection (GTR) rate of 44%. GTR (adjusted OR = 16.346; p = .001) and nadir GH level on OGTT 7 days after surgery (GH-7, adjusted OR = 0.660, p = .039) showed predictive significance for remission after surgery. Tumor size and invasiveness as well as cavernous sinus invasion were risk factors for residual tumor. For invasive macro- or giant adenomas, 6 of 15 patients achieved long-term remission with SSA pre-treatment whereas none of the 18 patients without any preoperative treatment was endocrine controlled.

Conclusions: Acromegalic patients did not gain more benefits from SSAs pretreatment. But, pre-treatment with SSA could be recommended to patients with invasive macro- or giant adenomas for significant improvement in long-term remission. GTR and GH-7 could be significant predictors in postoperative management of macro- or giant adenomas.

1. Introduction

Growth hormone (GH)-secreting pituitary adenoma is the second most common functional pituitary adenoma besides prolactinoma [1]. It could lead to acromegaly among adults and gigantism in children. To distinguish from non-functional pituitary adenoma, GH-secreting adenoma is characterized by hypersecretion of GH and abnormally high level of insulin-like growth factor 1 (IGF-1). Furthermore, elevated circulating GH overproduced by somatotroph adenoma cells, and IGF-1 could lead to acral overgrowth and soft tissue swelling as well as development of cardiovascular and respiratory disease, arthropathies and diabetes mellitus [2–4]. Accordingly, therapeutic goals for patients with GH-secreting pituitary adenomas are tumor removal as much as possible, restoration of normal GH secretory dynamics, normalization of IGF-1 level, and further decrease of the mortality caused by excessive GH [5,6]. At present, transsphenoidal adenomectomy (TSA) is the first-line therapeutic option particularly for patients with microadenomas

and non-invasive macroadenomas. Other therapeutic choices for GH adenomas include various medications such as somatostatin analogues (SSAs), GH-receptor antagonist and dopamine agonists (DAs), and radiosurgery.

Endocrinological assessment is crucial for all patients after therapeutic interventions. In 2000, the surgical remission was determined by a normal age- and gender-adjusted IGF-1 level and a nadir GH results on an oral glucose tolerance test (OGTT) of < 1 ng/mL [7,8]. But more recently, the criteria have been revised with the application of ultra-sensitive GH assays. And a more stringent cutoff point of nadir GH level in OGTT (0.4 ng/mL) was considered to be more beneficial in the aspect of mortality decrease [9]. Based on these criteria, it was reported that 60–75% of patients were endocrine controlled after surgery, but the overall remission rates decreased to 40-60% for macroadenomas and even 10-20% for invasive macroadenomas [10–12]. Several published case series had concluded some predictive factors for postoperative endocrine remission including tumor size, cavernous sinus invasion,

preoperative, intraoperative and postoperative GH levels [13–18]. Nevertheless, a few investigations about the topic focused on macro- and giant adenomas [13]. Owing to the relatively low remission rate, the management of macro- and giant adenomas remained a vital but unsolved issue in the existing literatures.

Somatostatin analogues (SSAs), including octreotide, lanreotide, and newly listed pasireotide, play an important role in the treatment of GH-secreting pituitary adenoma due to the relatively high effectiveness in both tumor shrinkage and serum GH reduction [19–21]. However, the effect of pre-surgical SSA treatment remained inconsistent over the past decades [22–25]. A prospective and randomized study showed that only macroadenoma benefited from the SSA pre-treatment [22]. However, others reported apparent advantage of SSA pre-treatment in all acromegalic patients [26,27]. Owing to the absence of consistent and robust evidence, SSA pre-treatment was recommended only for selected patients and patients with severe pharyngeal thickness, sleep apnea, or high-output heart failure in recent clinical guidelines for acromegaly [9].

Thus, to focus on preoperative predictors associated with postoperative endocrine remission and the efficiency of pre-surgical SSA treatment in macro- and giant adenomas, we retrospectively evaluated a large series of acromegalic patients operated at our institution that underwent long-term follow-ups.

2. Patients and methods

2.1. Patient population

Medical records of patients operated for acromegaly from January 2010 to December 2016 at West China Hospital of Sichuan University were reviewed and collected. With strict selection, a total of 100 patients met the following criteria (Fig. 1). The patients were newly diagnosed cases with macro- or giant adenomas who underwent surgery, either via transcranial or transsphenoidal approach; each patient was followed up for at least 6 months after surgery; OGTTs were preoperatively and postoperatively performed; patients who received preoperative radiosurgery were excluded, if any; patients treated with SSA before six months postoperatively were also excluded from this study considering the interference in long-term remission. As a result, 38 patients received somatostatin analogues (SSAs) injection, octreotide long-acting release (LAR, 20mg/ 28 days) or Lanreotide Autogel (40mg/ 14 days), before surgery for at least one month. And there was no dosage adjustment during the duration of pretreatment.

2.2. Neuroradiological evaluation

MR images (MRIs) were performed using standard 3.0-T scanner with contrast enhancement preoperatively and within 72 h postoperatively. However, MRIs without contrast enhancement were also unintentionally employed in preoperative neuroradiological evaluation for a few patients. Serial MR follow-ups were acquired 3, 6 and 12 months after surgery and annually thereafter. And invasion of pituitary adenomas (PAs) were assessed based on Knosp classification system [28]. Knosp Grade 3 and 4 adenomas were defined as invasive PAs. Gross total resection (GTR) of PAs was verified through MRI examinations within 3 days or on 3 months postoperatively. According to tumor maximal diameter, PAs were categorized into microadenoma (< 1 cm), macroadenoma (< 4 cm) and giant adenoma (≥4 cm). And microadenomas were excluded from this study. In addition, tumor volume was calculated according to the formation: Volume = a × b × c ÷ 2 (a, b and c were the length, width and height of tumors, respectively) [29].

2.3. Endocrinological evaluation

OGTT, including serum GH levels in 0, 30, 60, 90, and 120 min after

ingestion of 75 g oral glucose, was preoperatively employed in each patient and 1 week, 3, 6 and 12 months after surgery, and annually thereafter. Serum GH and IGF-1 levels were measured by a chemiluminescent immunoradiometric assay (Roche Diagnostics, Basel, Switzerland). Besides, GH index was calculated as following formation (GH index = preoperative nadir GH level ÷ tumor vulome).

2.4. Postoperative endocrine remission

Postoperative endocrine remission was verified when the serum GH nadir after an OGTT was < 1 ng/mL and normal serum IGF-1 level adjusted by age and gender. Short-term and long-term remissions were determined according to endocrinological studies at 3 and 6 months after surgery, respectively. In general, for patients with residual tumor or persistent GH hypersecretion, adjuvant gamma knife surgery (GKS) was recommended after assessment at the third month after surgery.

2.5. Pathological study

Intraoperative surgical specimens were verified by routine H&E staining and further immunohistochemistry (IHC) for GH, prolactin (PRL), adrenocorticotropin (ACTH), thyrotropin (TSH), luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

2.6. Statistical analysis

Data were displayed in the form of mean ± standard error of the mean (SEM) for normal distributed data or median for skewed distributed data. Chi-square or Fisher's exact tests were used for comparison of categorical variables whereas Student's T and Mann-Whitney tests were used for continuous variables. Receiver-operating characteristic (ROC) curve was performed to verify the predictive ability of preoperative and postoperative nadir GH levels for short-term and long-term surgical remission by comparing the area under the ROC curve (AUC). The relationship of nadir GH reduction (%) with underlying predictive variables in patients pre-treated with SSA was analyzed by Spearman rank correlation. Binary logistic regression was employed for analyzing independent predictive variables of remission rate as well as GTR rate. When p values were <.05, the differences were considered statistically significant. Statistical analyses were performed with SAS 9.2 software (SAS Institute, Inc, Cary, North Carolina).

3. Results

3.1. General characteristics

With a female predominance, 68 female and 32 male patients were enrolled in this study with the mean age at diagnosis of 40.6 ± 0.92 years (Table. 1). Macroadenoma accounted for 96% of this series and 4 were giant adenoma. Accordingly, the median tumor volume was 3.29 cm^3. Three of the masses were classified as Knosp Grade 0, 36 as Grade 1, 28 as Grade 2, 21 as Grade 3, and 11 as Grade 4. Thus, invasive PAs accounted for 32% of the whole cases. Seventy lesions (70%) were complete solid, but cystic components presented in 30 patients. Of the series of cases, 96 cases were treated by transsphenoidal microscopic adenomectomy and transcranial approach was performed in remaining 4 cases. As a result, gross total resection (GTR) was accomplished in 44 cases.

3.2. Pretreatment with somatostatin analogues

In this study, 38 patients were pre-treated with SSA (Octreotide LAR, 12 cases; Lanreotide Autogel, 26 cases) for at least one month preoperatively (median, 3 months; range, 1~13 months). The initial dosage of Octreotide LAR and Lanreotide Autogel were 20mg and 40mg for each patient, respectively. Significant volume reduction (> 20%)