Effect of Cabergoline Treatment on Disease Control in Acromegaly Patients

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ABSTRACT

The aim of this study was to evaluate the efficacy of cabergoline in normalizing plasma IGF-I levels in acromegaly patients with elevated IGF-I levels after surgery and/or SRL therapy. Acromegaly patients (n: 143) were evaluated retrospectively. Patients with elevated IGF-I levels after surgery and/or SRLs therapy and a fixed dose of SRLs treatment for the last six months with no history of radiotherapy in the last three years were included in the study (n: 12). Previous treatment regimens, baseline PRL and IGF-I levels (ULNR), sella MRI, and immunohistochemical findings were evaluated. Cabergoline was used as an add on (n: 11) or single medical treatment (n: 1). The median duration of treatment with SRL alone was 12 months (range 6–48 months). The mean IGF-I value before cabergoline therapy was 1.45 ± 0.4 ULNR. The mean cabergoline dose and duration of treatment were 1.55 ± 0.75 mg/week and 9 ± 6.3 months, respectively. IGF-I normalization was only achieved in patients with serum IGF-I concentration $< 1.5 \times$ ULNR before the onset of cabergoline treatment (n: 9). In some of the patients with IGF-I normalization, baseline prolactin levels were normal (n: 3). Immunopositivity for prolactin in adenoma tissue was found in three patients with IGF-I normalization. Cabergoline therapy is effective in the normalization of IGF-I levels even in normoprolactinemic acromegaly patients when IGF-I levels are mildly or moderately elevated during SRL therapy.

Introduction

Acromegaly is a chronic disease associated with somatic and metabolic effects due to long-term exposure to increased growth hormone (GH) and insulin like growth factor 1 (IGF-I) levels. The prevalence and annual incidence of acromegaly was previously reported as 60/1 000 000 and 3.3/1 000 000, respectively [1]. However recent studies have revealed higher incidence and prevalence rates (11/1 000 000/year and 130/1 000 000, respectively) [2–4]. The excess production of GH is due to a pituitary adenoma in more than 95 % of acromegaly cases and the tumor is defined as a macroadenoma in approximately 75 % of patients. Approximately 30 % of these patients present with hyperprolactinemia caused either by prolactin co-secretion or presence of stalk compression due to the pituitary adenoma [5].

The mortality rate in patients with acromegaly is 2–3 times higher compared to the general population with a similar age and sex distribution. The most common causes of mortality are reported as cardiovascular, cerebrovascular, respiratory diseases, and malignancies [6]. However later studies have demonstrated a reduction in mortality rates with successful clinical control [7] and it has

been shown that reduction of GH/IGF-I levels to the normal range is associated with a reversal of mortality rates in acromegaly patients to a similar ratio expected for the general population. Nevertheless, the cut off value for GH/IGF-I levels at which the risk returns to normal is controversial [8]. Normalization of IGF-I is also a very important indicator in disease control and reduction of disease-related comorbidities [9]. Treatment targets are normalization of GH and IGF-I levels, control of the tumor mass, reduction of mortality, management of comorbidities, preservation of pituitary function, and attenuation of symptoms [10].

Treatment options for acromegaly include surgery, medical therapy, and radiotherapy (RT). Transsphenoidal pituitary surgery is the preferred first-line treatment. Unfortunately, remission may not be achieved in approximately 25% of patients with microadenomas and in 40–60% of patients with macroadenomas [11]. These patients require adjuvant medical treatment and/or RT. The first-line drugs in medical therapy are first generation somatostatin receptors ligands (SRLs); octreotide (OCT) and lanreotide (LAN) [10]. The biochemical control rates with first generation SRL octreotide extended release (OCT-LAR) and lanreotide autogel are approximately 55% [12]. However, the effectiveness varies from 25% to 70% in different studies and features regarding age, sex, baseline GH and IGF-I levels, tumor volume, somatostatin receptor (SSTR) expression and subtypes (SSTR2, SSTR5), dopamine receptor status and granulation pattern are considered important predictors of treatment response [13–15]. Other alternative treatment options are second-generation somatostatin analogues (pasireotide), GH receptor antagonist (pegvisomant), and dopamine agonists (DAs) [16].

Dopamine, which is a neurotransmitter synthesized in the hypothalamus, inhibits pituitary growth hormone secretion through the dopamine subtype 2 receptor (D2R) [17]. The majority of adenohypophyseal adenomas have the D2R hetero oligomerization of dopamine receptor 2 and somatostatin receptor 2 that may enhance functional activity [18]. Dopamine agonists are recommended as first-line medical treatment in patients with mildly elevated IGF-I and GH after surgery and may also be used in combination with SRLs in patients who are partially resistant to SRLs treatment. IGF-I normalization is achieved in 35% of patients treated with cabergoline (CAB) monotherapy and in approximately 50% of patients treated with combination therapy with SRLs [19].

The aim of this study was to evaluate the efficacy of treatment, alone or in combination with SRLs therapy, on normalizing plasma IGF-I levels in acromegaly patients with active disease after first line treatment modalities.

Subjects and Methods

Acromegaly patients (n: 143) who were being followed-up at the endocrinology outpatient clinic of Istanbul Medical Faculty between 1980–2020 were evaluated. DAs were used in the treatment of 34 patients. Patients with elevated IGF-I levels after surgery and/or SRLs therapy and a fixed dose of SRL treatment for the last six months with no history of radiotherapy in the last three years were included in the study (n: 12) (▶ Fig. 1). The time frame of the study cohort was 1989–2019. Treatment protocol of the patients that are included in the study is summarized in ▶ Table 1. Response to DAs therapy was defined as normalization of plasma IGF-I levels

based on sex and age of the patients. IGF-I level was expressed as upper limit of age adjusted normality ratio (ULNR).

Patients' clinical features regarding sex, age, baseline PRL and IGF-I concentrations at the time of diagnosis, MRI findings, previous treatment modalities, presence and size of postoperative residue, dose and duration of SRLs treatment, IGF-I level (ULNR) before onset of DA therapy, dose and duration of DA treatment, achievement of IGF-I normalization were evaluated retrospectively. GH and IGF-I were measured using two-site chemiluminescent immunometric assay (IMMULITE 2000). The sensitivity of the assay was 0.01 ng/ml for GH levels. Serum PRL levels were measured using an electrochemiluminescent immunoassay (ECLIA), with normal ranges for adult males and females of 4.04–15.2 ng/ml and 4.7–23.3 ng/ml, respectively. High plasma prolactin levels were reevaluated with Polyethylene glycol (PEG) precipitation test in order to exclude presence of pseudohyperprolactinemia, also presence of medications associated with hyperprolactinemia, pregnancy, lactation, chronic kidney and liver disease and hypothyroidism were excluded. The pathology specimens of pituitary adenomas were revised by the same pathologist concerning their immunohistochemical (IHC) staining patterns. Histopathological findings are classified as densely or sparsely granulated; a densely granulated somatotroph adenoma was defined as diffuse and strong immunoreactivity with GH and perinuclear staining with low molecular weight keratin (LMWK); sparsely granulated somatotroph adenoma was defined as weak and focal immunoreactivity with GH and juxtanuclear globular immunoreactivity with LMWK. A densely granulated prolactinoma was defined with the composition of acidophilic to chromophobic cells with abundant and diffuse cytoplasmic PRL granules and a sparsely granulated prolactinoma was defined with extrusion of secretary granules along the lateral cell surfaces into the extracellular space, which has been regarded as a specific feature of the sparsely granulated prolactinoma [20, 21]. In pituitary adenomas with mixed GH and PRL secretion granulation patterns regarding GH and Prolactin staining are indicated separately.

This study was approved by the Clinical Ethics Committee of Istanbul University, Istanbul Faculty of Medicine and performed in accordance with the Helsinki recommendations. The study involved human participants and written informed consent was obtained from all of the participants. Statistical analyses were performed using SPSS version 21.0. Categorical variables were presented as frequency and percentage, whereas numerical variables were presented as mean ± standard deviation (SD).

Results

Twelve patients were included in this study (F: 7, M: 5). The mean age of the patients was 37 ± 9.9 years (range 24–56 years). On initial evaluation two patients had microadenoma and eight patients had macroadenoma, adenoma size was not available in two of the patients. Mean IGF-I value before the initiation of SRL was 2.41 ± 0.78 ULNR. The median duration of treatment with SRL alone was 12 months (range 6–48 months). The mean IGF-I value before the initiation of CAB therapy was 1.45 ± 0.4 ULNR (range 1.05–2.66). The mean dose and duration of CAB treatment was 1.55 ± 0.75 mg/week (range 0.5–3.5 mg/week; median 1.5 mg/week) and 9 ± 6.3
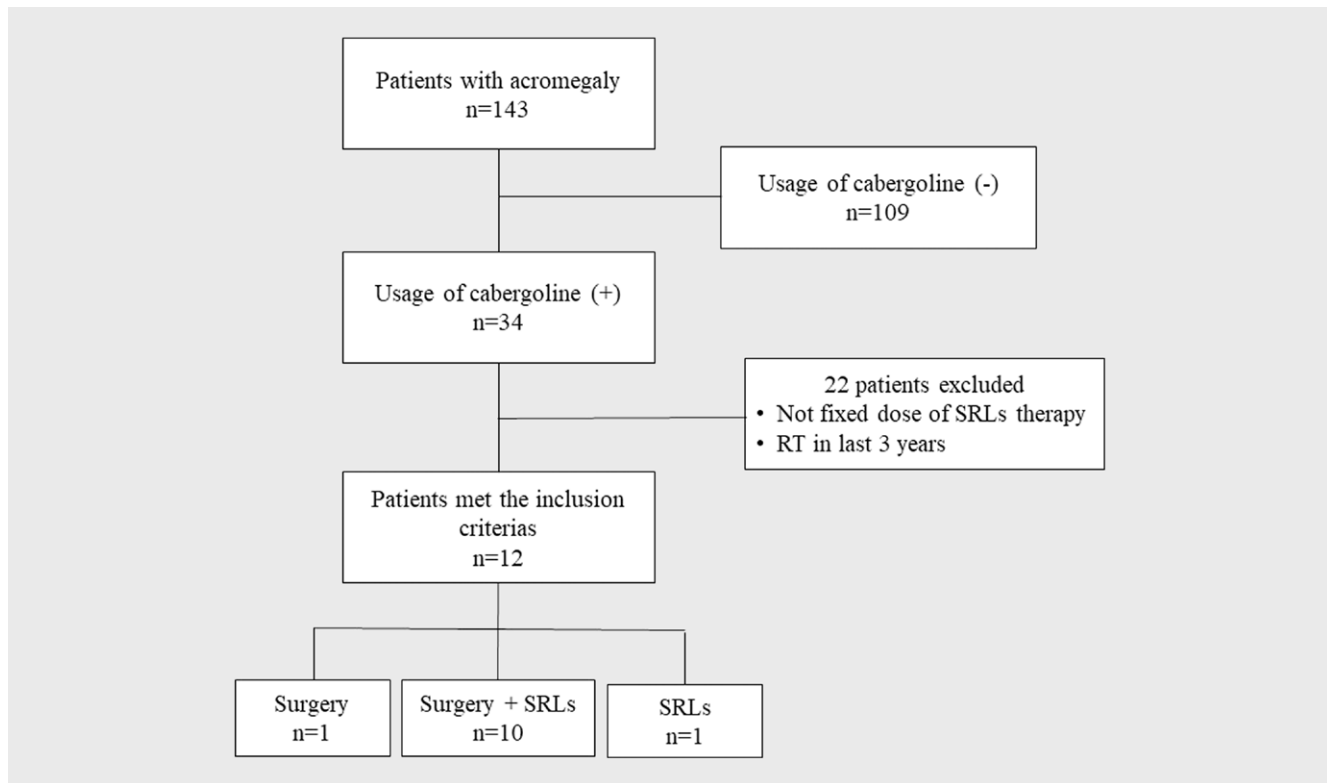
▶ **Fig. 1** Flow diagram of case selection.

months (range 3–19 months; median 6.5 months), respectively. One patient with McCune Albright syndrome was treated with primary medical therapy with SSL prior to DA therapy (▶ **Fig. 1**). IGF-I normalization was achieved in nine patients, all of which had a serum IGF-I concentration < 1.5 × ULNR before the onset of CAB treatment.

IHC analysis had been performed in nine of our patients and PRL staining was positive in four of these patients (IHC staining patterns in the pathological specimens are shown in ▶ **Fig. 2**). In our patients with poor treatment response, two patients (case 8 and 10) had negative PRL staining, and one patient (case 9) had positive prolactin staining with densely granular pattern. Ki67 was 3 % and before CAB therapy IGF-I value was 2.66 ULNR in case 10; although normalization of IGF-I could not be achieved in this patient, there was a reduction of 28 % in the serum IGF-I level in the sixth month of CAB treatment. Among five patients who presented with hyperprolactinemia, three patients tested positive for PRL. In the IGF-I normalized group, IHC staining results were available for six patients, and immunopositivity for PRL was found in three of these patients (▶ **Fig. 2**). Patients' response to treatment and clinical features regarding baseline IGF-I and prolactin levels, MRI findings, size of adenoma, immunohistochemical results, previous treatment modalities, dose and duration of CAB treatment is demonstrated in ▶ **Table 1**.

Discussion

Our results support the use of CAB in combination with SRLs on normalizing plasma IGF-I levels in acromegaly patients with active disease after first line treatment modalities. CAB is commonly used in the treatment of acromegaly; however, in studies evaluating its effectiveness, quite different results have been obtained. The efficacy of CAB varies widely according to dose and duration of treatment, plasma IGF-I, GH levels and presence of concomitant hyperprolactinemia and identification of suitable candidates for CAB treatment remain to be determined. In the study of Abs et al., a good treatment response (IGF-I < 300 ng/ml) was obtained in 39 % of patients treated with CAB and doses ranged from 1 mg to 3.5 mg per week with a mean dose of 3.3 mg/week, which was higher than the rest of the studies in the current literature data [22]. It was shown that the efficacy of CAB is associated with PRL cosecretion and plasma levels of IGF-I and GH [22].

In a meta-analysis by Sandret et al., it was shown that the efficacy of CAB treatment when used as a stand-alone therapy depends on the baseline IGF-I and PRL levels and the duration of treatment. If IGF-I level is slightly elevated prior to initiation of CAB treatment, the possibility of IGF-I normalization increases. The rate of achieving a normal IGF-I level with CAB treatment was approximately 50 % when IGF-I was less than 1.5 ULNR, and 30 % when IGF-I was over 1.5 ULNR. In this meta-analysis, the mean CAB treatment dose was 2.5 mg/week (range of 0.5–7 mg/week) [19]. In the other group of the study, when CAB was used in combination with SRLs, IGF-I normalization was achieved in 52 % of the patients. The mean CAB

Table 1 Clinical, biochemical and immunohistochemical features of study group during acromegaly management.

No	Age at diagnosis	Sex	Baseline PRL (ng/ml)	IGF-I ULNR	Baseline IGF-I (ng/ml)	Baseline MR	Postoperative residue	Postoperative IGF-I ULNR	SRL dose (mg/month)	Duration of SRL therapy (month)	IGF-I (ULNR) before CAB	Dose of CAB (mg/week)	Duration of CAB therapy (month)	IGF-I normalization	Immunohistochemical analysis
1	30	F	77	3.2	1078 (329)	20×17 mm T2 hypointens	No	2.88	OCT LAR 30	8	1.45	1	7	Yes	GH (+) sparsely granulated PRL (+) PIT 1(+) LH (−) FSH (−) TSH (−)
2	35	F	35	3.6	1400 (382)	27.5×24mm cavernous sinus invasion	>1cm	N/A	OCT LAR 30	12	1.21	2	8	Yes	GH (+) densely granulated PRL (−)
3	37	F	6	4.5	1393 (307)	14×7 mm T2 hypointens	>1cm	3.55	OCT LAR 30	7	1.08	1	3	Yes	GH (+) densely granulated, PRL (−) ACTH (−) TSH (−)
4	24	M	NA	NA	NA	NA	No	N/A	OCT LAR 30	48	1.13	2	19	Yes	NA
5	51	F	NA	1.86	347 (186)	8×5 mm T2 hyperintens	No	2.23	OCT LAR 30	6	1.48	1.5	19	Yes	GH (+) PRL (−) ACTH (−) Ki67 1%
6	37	F	NA	NA	NA	NA	>1cm	1.39	LAN LAR 90	32	1.3	0.5	3	Yes	NA
7	31	M	19	3.7	929 (246)	23×19mm	>1cm	3.4	LAN LAR 120	9	1.3	3.5	6	Yes	GH (+) PRL 5% (+) ACTH (−) TSH (−) FSH (−) LH (−) PIT 1(−)
8	40	M	16.8	4.56	1077 (236)	16×15mm	<1cm	2.74	LAN LAR 120	15	1.88	1.5	9	No	GH (+) densely granulated PRL (−),

▶ Table 1 Continued.

No	Age at diagnosis	Sex	Baseline PRL (ng/ml)	IGF-I ULNR	Baseline IGF-I (ng/ml)	Baseline MR	Postoperative residue	Postoperative IGF-I ULNR	SRL dose (mg/month)	Duration of SRL therapy (month)	IGF-I (ULNR) before CAB	Dose of CAB (mg/week)	Duration of CAB therapy (month)	IGF-I normalization	Immunohistochemical analysis
9	56	M	27	2.5	541 (210)	18 mm	<1 cm	1.66	LAN LAR 120	8	1.67	2	5	No	GH (+) sparsely granulated PRL (+) densely granulated TSH (−) LH (−) FSH (−) KI67 3 %
10	36	F	5.2	NA	NA	20 × 25 mm	>1 cm	2.11	OCT LAR 20	15	2.66	2	6	No (28 % decrease)	GH (+) PRL (−) FSH (−) LH (−) TSH (−) ACTH rare (+)
11	50	F	16	2.8	587 (209)	10 × 11 mm	no	1.2	–	–	1.2	1	4	Yes	GH (+) sparsely granulated PRL (+) densely granulated ACTH (−) LH (−) FSH (−) TSH (−)
12	27	M	13	1.7	572 (329)	6.5 mm	–	1.7	LAN LAR 120	48	1.05	1	19	Yes	Primary medical therapy

* Surgery was performed in all patients except case 12. ULNR: Upper limit of normal ratio; NA: Not available.
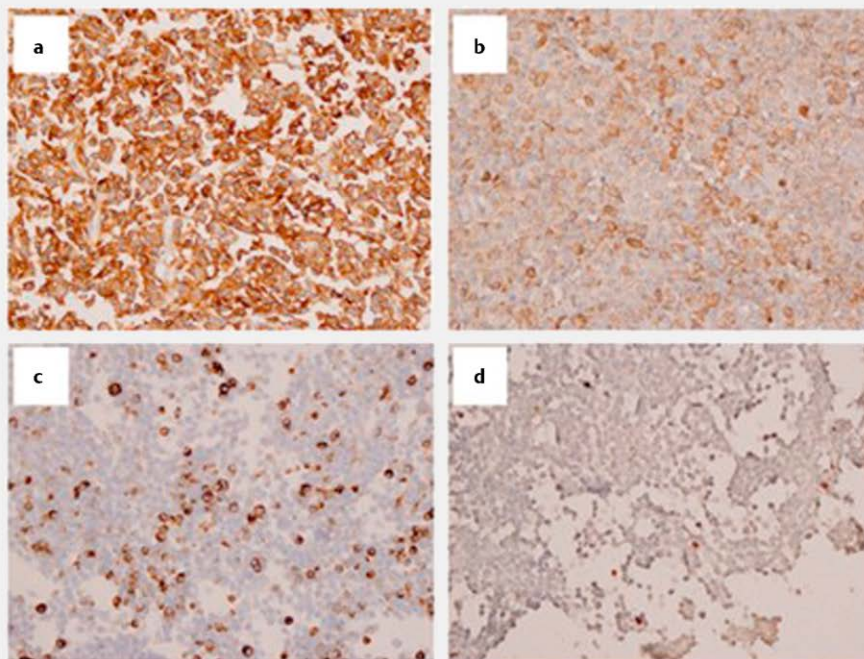
► **Fig. 2** Immunohistochemistry (GH, PRL, and Ki67) of GH-secreting pituitary adenomas: Immunohistochemistry (GH, PRL, and Ki67) of GH-secreting pituitary adenomas. **a**: Densely granulated GH expression (40×). **b**: Sparsely granulated GH expression (40×). **c**: Sparsely granulated PRL expresssion (40×). **d**: Ki67 proliferation index 3% (40×).

treatment dose was 2.5 mg/week (range of 1–7 mg/week). The efficacy of CAB was associated with baseline IGF-I level, but there was no correlation with dose and duration of therapy or PRL level. The baseline IGF-I level before CAB therapy was 1.45 ULNR in the normalized group, while it was 2.22 ULNR in the non-normalized group [19]. Similarly in our study, patients whose IGF-I levels were normalized with DA and SRL combination therapy, plasma IGF-I values were under < 1.5 ULNR before CAB therapy. Among patients who responded to DA treatment, the highest IGF-I level was 1.48 ULNR (case 5). The patients whose IGF-I values remained high after DA treatment had IGF-I values which were above > 1.5 ULNR. IGF-I levels among cases 8, 9 and 10 were 1.88 , 1.67 and 2.66 ULNR, respectively.

In the study of Vilar et al., among acromegaly patients who had partial response to long-term SRL treatment, in 40% of the patients, IGF-I normalization was achieved with low-dose CAB treatment (mean 2.19 ± 0.64 mg/week). It was shown that the most important predictor of response to treatment was IGF-I level and this response was independent of prolactin staining in IHC examination and plasma prolactin level. IGF-I normalization was not achieved with CAB combination therapy in any of the patients with IGF-I levels above 2.5 ULNR [23]. In the study of Mattar et al., IGF-I normalization was achieved in 64% of patients with the addition of CAB to SRL treatment in patients with IGF-I value < 2.2 ULNR. IGF-I was normalized in 1of 6 patients (17%) with IGF-I ≥ 2.2 ULNR. There was no correlation between immunopositivity for PRL and response to CAB treatment [24].

In one of three patients who did not respond adequately to treatment, immunostaining in adenoma cells was densely granulated for prolactin, whereas sparsely granulated for GH and Ki 67 index was 3%. All of these features predict a poor response to treatment. Case 10 presented with an IGF-I level over > 2.2 ULNR before CAB treatment. This value was also an indicator of poor treatment response in our study.

The mean dose of CAB used in our study was 1.55 ± 0.75 mg/week (range 0.5–3.5 mg/week median 1.5 mg), and it was used in a relatively lower dose compared to other studies in the literature. In recent publications, the dose recommendation for CAB in the treatment of acromegaly is 0.5–2 mg/week [25]. Previous studies have indicated that, the efficacy of cabegoline was associated with PRL cosecretion when used as a stand-alone therapy, but no correlation was found between treatment efficacy and PRL level in combination treatment with SRLs [19]. It is suggested that the efficacy of combination therapy is not only additive, but there is also the synergistic effect of the SSR-5/DR2 heterodimer structure [18, 26]. Cabergoline (CAB) treatment in patients with Parkinson's disease has been previously found to be associated with increased risk of cardiac valve regurgitation, which has caused a similar concern for the use of these agents in acromegaly patients. However current literature results failed to detect a similar relation in these patients, cabergoline treatment was not associated with detrimental effects on cardiac valves [27] and it is considered as a well tolerable treatment modality for acromegaly patients [19]. Recently impulse control disorders presenting with symptoms such as compulsive shopping, pathologic gambling and hypersexuality has also been reported with DA treatment in patients with hyperprolactinemia [28], however similar conditions related with this side effect were not reported in our patients.

The limitation of our study is that the sample size was small due to the fact that it is a rare disease and study groups were selected from patients who had been receiving a fixed dose of SSAs treatment for the last six months. Fixed-dose SRLs therapy is also a factor that increases the power of the study.

In conclusion, addition of CAB is efficacious in control of IGF-I levels in acromegalic patients with mild/moderately elevated IGF-I levels during SRLs therapy. CAB may be an effective treatment in these patients. Considering the benefit of cost effectiveness, octreotide and CAB combination therapy should be kept in mind prior to other treatment modalities in these patients.

Acknowledgements

Conflict of Interest

The authors declare that they have no conflict of interest.

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