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Duhok acromegaly; a prospective cohort study

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Abstract

Background and objectives: Acromegaly is a rare hormonal disorder; the prevalence is around 60 cases/ million population, incidence is3.3new cases/million/year. Mortality rate 2 to 4 times that of general population. It is usually the result of a somatotrope adenoma in more than 95% of cases.The aim is to study our patient s characteristics, to identify the best management for acromegaly, which can induce clinical, and biochemical remission, also this paper aimed to increase acromegaly awareness regarding the importance of early diagnosis of this disease. **Methods:** This is prospectivecohort study involving 15patients; the duration of study is 2 years (June 2015-June 2017). All patients diagnosed by high level of insulin-like growth factor 1 followed by growth hormone suppression test and MRI of pituitary gland. Those patients underwent transsphenoidal resection, diagnosis confirmed by histopathology too. **Results:** The median age of patients at presentation was 47.3 (SD 9.9), with majority between 40-50 years. Females constitute 8 of the patients, while number of males was 7. The most common chief complaint was headache accounting for 40% of cases. All patients at presentation were suffering from macroadenoma.The combination of surgical and medical treatment was more successful in reducing GH and IGF1 levels in comparison to medical treatment alone (p value of <0.001 and 0.037 respectively). **Conclusions:** The combination of surgical and medical treatment was superior to medical treatment alone in reducing GH , IGF1 level and inducing tumor remission.The two dilemmas we are facing here in Duhok are: First; delayed diagnosis as reflected by the fact all of our patients were macroadenoma at presentation, that is why we need to increase awareness about this disease and the importance of early diagnosis and early referral before onset of complications which directly associated with increase mortality. Secondly; low compliance for medical treatment, to improve this we need to provide free measurements of both GH and IGF1 levels for all patients receiving somatostatin analogue treatment.

Key words: Acromegaly;Duhok.

Introduction

Acromegaly is a rare hormonal disorder; the prevalence is around 60 cases/million population[1], the incidence is 3.3 new cases/million/year[1]. However; recent study from Belgium showed a higher incidence of approximately 13 per 100,0002. These results indicate that acromegaly maybe underdiagnosed.It is usually the result of a somatotrope adenoma in more than 95% of cases[2]. Acromegaly affects males and females equally, and the mean age at the diagnosis is 45years[3-6].

A proportion of patients with acromegaly presented due features related to acral enlargement, that is why menstrual disturbance may be the most frequent presentation in women5 (Table 1). In review involving 164 patients with acromegaly, 34% of them presented with features related to acromegaly, this include bitemporal hemianopia, carpal tunnel syndrome and headaches[7]. The rest 50 patients were seeking medical advice due to a complaint unrelated to acromegaly[7]. As acromegaly progress very slowly, the diagnosis is usually delayed for 7-10 years after the estimated onset of symptoms8. That is why it is necessary to increase awareness about constellation of signs and symptoms of acromegaly in order to detect cases earlier before onset of complications, as mortality rate is 2 to 4 times higher than general population6. The target group include doctors working in orthopaedists, otorhinolaryngologists, rheumatologists, cardiologists, dentists, and most importantly primary care physicians9.In 75% of patients with acromegaly, the initial MRI shows macroadenoam (>10mm), due to late diagnosis, while the remaining 25%, its microadenoam (<10mm), this carries better prognosis as it is likely to be curable by surgery[10].Macroadenoma causes pressure effect on adjacent tissues, such as compression of the optic nerve, can lead to loss of vision[11]. All in all, acromegaly has a wide spectrum of comorbidities, which cause significant serious clinical manifestations; therefore, as the diagnosis of acromegaly is delayed more, these consequences will be more serious. This shows the importance of acromegaly awareness campaigns[12].

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Table (1): Clinical Features of Acromegaly

Feature	%
Acral enlargement	86
Maxillofacial changes	74
Excessive sweating	48
Arthralgias	46
Headache	40
Hypogonadal symptoms	38
Visual deficit	26
Fatigue	26

Patients and methods

The population of this prospectivecohort study consisted of a total 15 patients diagnosed with acromegaly from1st June 2015 to 1st June 2017, who come for follow up in the endocrine clinic at Azadi General Teaching Hospital. The informed consent was taken from every patient after full explanation of the study; which was performed under medical ethics.The detailed history of all such patients was taken and complete physical and relevant clinical examination was performed.A specially-designed questionnaire was used to obtain information from participants. Inclusion criteria include patients already diagnosed with acromegaly, however the diagnostic parameters for acromegaly were also kept in mind i.e. on the basis of clinical (gross of features of acromegaly), and biochemicalraisedinsulin-like growth factor 1 (IGF1)levels, which matched for age and sex 13-14, confirmation of acromegaly done by GH suppression test, followed by MRI of pituitary gland for localizing adenoma.Those patients underwent transsphenoidal resection, diagnosis confirmed by histopathology too. Growth hormone(by Cobas 6000) and IGF1 (by Elisa) measured before and after treatment.Criteria used to define remission of acromegaly were according to American Association of Clinical Endocrinologist (AACE), which includes clinical remission(absence of headache and sweating with controlled blood pressure), normalization of IGF1 level, random GH<2.5 ng/mL and GH<1ng/mL during an OGTT15,16.All data were analysed using the Statistical Package for Social Science (SPSS); Spearman`s correlation test was used for comparison of IGF1levels before and after treatment, while pairedstudent t- test was used to assess differences in GH between the groups. P values less than 0.05 were considered significant.

Results.

The median age of patients at presentation was 47.3(SD of 9.9), with majority of patients between 40-50 years as shown in figure 1. Females constitute 8 of the patients, while number of males was 7 as shown in Table 2. All patients at presentation were suffering from macroadenoma, 7(46%) of them were suffering from hypertension, 5(33%) diagnosed with diabetes mellitus, 7(46%) with impaired glucose tolerance,4(26%) from congestive heart failure (CHF) and 4(26%) patients were suffering from hypopituitarism as shown in table 2, mixed (with prolactinoma) diagnosed in 4(26%) patients.Type of treatment used in treatment of acromegaly was: A- combination of medical and surgical in 60% of cases, B- medical alone (nonoperable) was used in 26% , C- those who prepared for surgery by Somatostatin analogue (neoadjuvent) were 13% as shown in Figure 2.

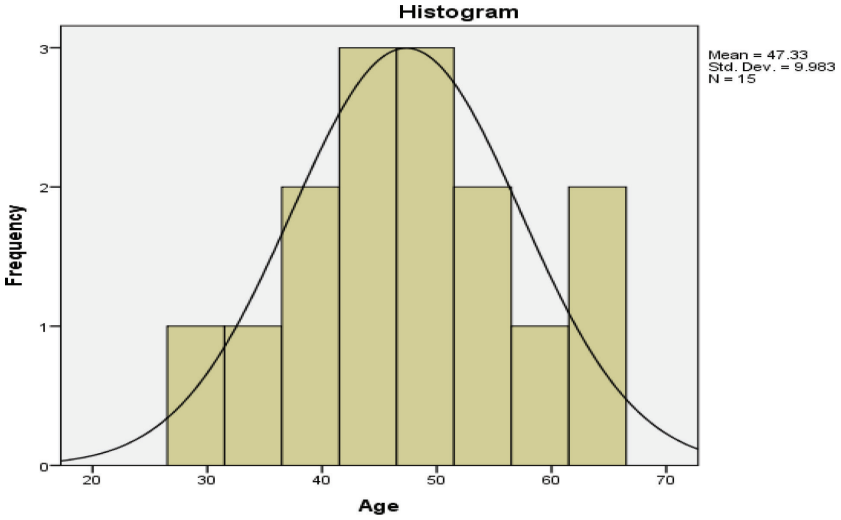

Figure (1):Age at presentation. Median age at presentation was 44.7 (SD 9.9.).

Table (2): Patients characteristics of Duhok acromegaly.

Patients Characteristics	No. (%)
Male Gender	7(46%)
Female Gender	8 (53%)
Median Age at presentation	47.33
Macroadenoma	15
Microadenoma	0
Hypertension	7(46%)
Diabetes	5 (33%)
Impaired glucose tolerance(IGT)	7(46%)
CHF	4 (26%)
Mixed (with prolactinoma diagnosed by histopathology)	4(26%)
Hypopitutarism before surgery	4(26%)
Transient diabetes insidious as complication of surgery	7 (46%)

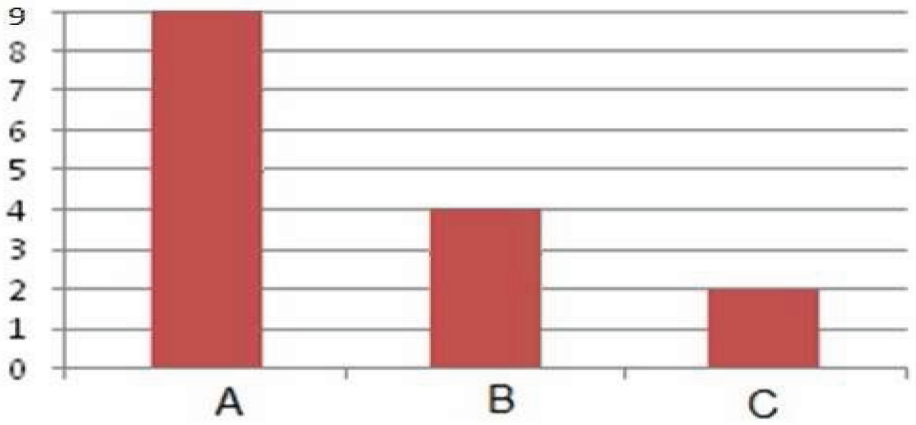

Figure (2):Type of treatment used in Duhok acromegaly patients, A: Combined Somatostatin analogue and surgery (60%), B: medical alone (Nonoperable) 26%, C; prepared for surgery by Somatostatin analogue (Neoadjuvent) 13% (note, total number of patients, who used combined medical and surgical treatment was 11).

The most common chief complaint was headache accounting for 40% of cases followed by acral enlargement 26%, while the rest 33% of patients presented with other features (hypogonadism, fatigue, visual field defects and arthralgia) as shownin Table 3andFigure 4.Total number of patients achieving remission was 10 (66%), however 40% of those underwent remission relapse again and they needed medical treatment as shown in Table 4.Growth Hormone levels measured before and after treatment (medical and surgical vs. medical alone), the combination of surgical and medical treatment was superior to medical alone ($p < 0.001$), t -6.561, the mean of GH before treatment (surgical and medical)is 24.73 (SD 6.035), while the mean of GH after treatment (surgical and medical) is 1.827 (SD 2.1114) .The mean of GH before treatment (medical alone) is 29.00 (SD 2.944), while the mean of GH after treatment (medical alone) is 13.000 (SD 4.6904)as shown in figure 3.IGF1 level also measured before and after treatment (medical and surgical vs. medical alone),the combination of surgery with and medical treatment was more successful in reducing IGF1 levels in comparison to medical treatment alone with p value of 0.037 ($r2 = 0.54$), as shown in figure 4.

Table (3): Frequency distribution of clinical features of Duhok acromegaly

Presenting Clinical Features	No. (%)
Headache	6 (40%)
Acralenlargment	4 (26%)
Others	5(33%)
• Arthralgias	1
• Hypogonadal symptoms	1
• Visual deficit	2
• Fatigue	1

Table (4): Frequency distribution of patients achieving remission.

Treatment modality	No. of patients	No. of underwent remission
Combination of medical and surgical (including neoadjuvent)	11	10 (90%)*
Medical alone(non-resectable tumor)	4	0 (0%)
Overall	15	10 (66%)

* Note, 6 patients (40%) relapsed after remission

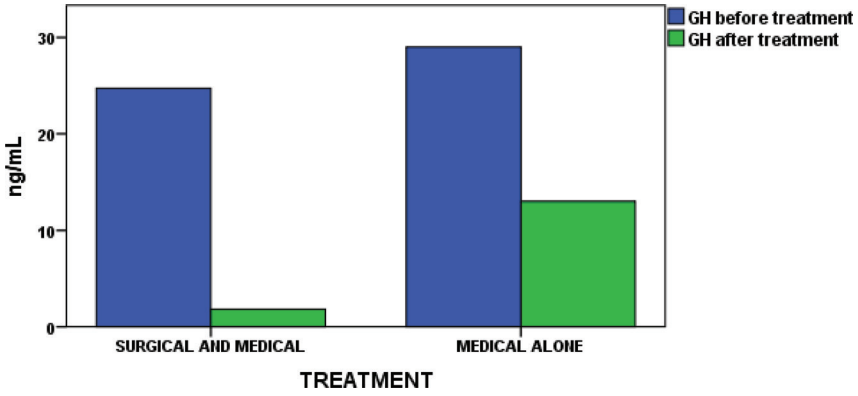

Figure (3): Growth hormone levels before and after treatment (medical and surgical vs. medical alone).

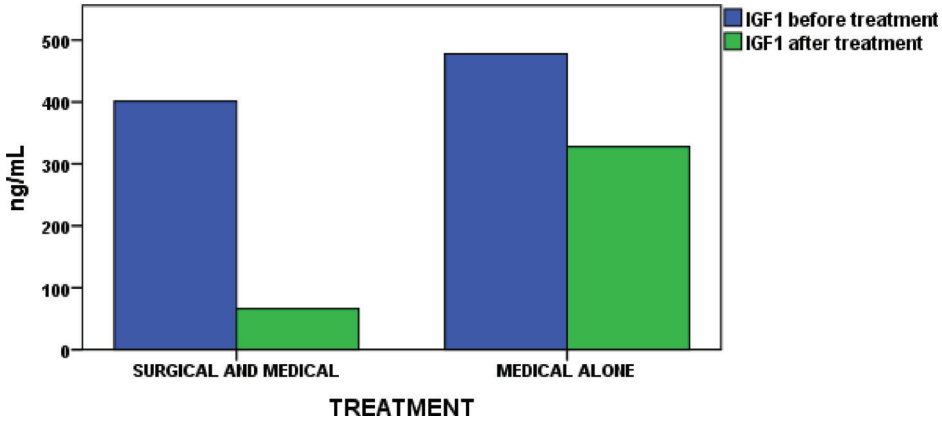

Figure (4): IGF1 levels before and after treatment (medical and surgical vs. medical alone), surgical and medical treatment was superior to medical treatment alone with p value of 0.037 (r2= 0.54).

Discussion

Our results show no significant difference between males and females regarding development of acromegaly and the main age at presentation was in mid 40s, and this is in agreement with most literatures[17-20]. The most common clinical presentation of our patients was headache followed by acral enlargement, while in other studies acral enlargement account for majority of presentations[7], Table 1,this can be explained by fact it was true all of our patients have some gross featuresof acromegalyon examination (somatic features)[21-24], it wasn't their chief complain as the awareness regarding this disease among public is poor.All patients at presentation were suffering from macroadenoma, as acromegaly is insidious onset and it needs 7-10 years to present8, while in other studies, macroadenoma (>10mm) account for 77% of cases[10]. Presence of higher number of patients with macroadenoma at presentation indicates the awareness about early detection of this disease among medical staff is lower. Our patients have high incidence of diabetes, hypertension, hypopituitarism, visual field defects,arthropathyand CHF, this indicate the advance stage of disease at presentation[25-31].The aim of treatment is to remove/ control tumour, restore GH secretion to normal, reduce IGF-I levels to normal and controlling symptoms, this can be achieved by surgical removal of the tumour, drug therapy or radiation therapy of the pituitary. Surgery is considered first-line therapy[32-39]; drug therapy may be used as a pre-operative treatment or as primary medical therapy in non-resectable tumours or when tumor relapses. The GH and IGF reduced significantly if combination of surgery and medical treatment used in comparison to medical treatment alone (Figure3, 4), this approach used by our centre when approaching these patients, we prepared 2 patients for surgery by medical treatment in form of somatostatin analogue (figure 2)as access to neurosurgeon take time and when tumor relapsesposoperatively, medical treatment used again. As far as all our patients were diagnosed with macroadenoma, a significant residual tumour often remains after surgery, usually patients need medical treatment also to achieve symptoms relieve and achieving IGF1and GHlevels[40-43]. While dopamine agonists used in conjunction with somatostatin analogue in subset of patients who are resistant to somatostatin[44]. Definition of remission in acromegaly is random fasting mean GH <2.5ng/mL, GH< 1 ng/mL during an OGTT with normal IGF-1 level. While not controlled acromegaly is defined as: GH ≥1ng/mL with IGF-1 level above normal range for sex and age15-16. Total number of patients underwent remission were 66%, however during follow up of these patients who underwent remission 40% relapse (Table 4) this indicates that acromegaly is a chronic disease and may need regular follow up for any recurrence even for those who fill criteria of cure.

Conclusions

The combination of surgical and medical treatment was superior to medical treatment alone in reducing GH, IGF1 levels and inducing tumorremission. The two dilemmas we are facing here in Duhok are:First; delayed diagnosis as reflected by the fact all of our patients weremacroadenoma at presentation that is why we need to increase awareness about this disease among medical staff and the importance of early diagnosis and early referral before onset of complications which directly associated with increase mortality. Secondly; low compliance for medical treatment, to improve this we need to provide free measurement of both GH and IGF1 levels for all patients receiving somatostatin analogue treatment.

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References

1. Nabarro JD. Acromegaly. ClinEndocrinol (Oxf). 1987;26:481-512

2. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J ClinEndocrinolMetab. 2006; 91:4769- 4775.

3. Ezzat S, Forster MJ, Berchtold P, Redelmeier DA, Boerlin V, Harris AG. Acromegaly: clinical and biochemical features in 500 patients. Medicine (Baltimore). 1994; 73:233-240.

4. Molitch ME. Clinical manifestations of acromegaly. EndocrinolMetabClin North Am. 1992; 21:597-614.

5. Drange MR, Fram NR, Herman-Bonert V, Melmed S. Pituitary tumor registry: a novel clinical resource. J ClinEndocrinolMetab. 2000; 85:168-174.

6.Swearingen B, Barker FG II, Katznelson L, et al. Long term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J ClinEndocrinolMetab. 1998; 83:3419-3426.

7. Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R. Epidemiology of acromegaly in the Newcastle region. ClinEndocrinol (Oxf). 1980; 12:71-79.

8. Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK. Determinants of clinical outcome and survival in acromegaly. ClinEndocrinol (Oxf). 1994; 41:95- 102.

9. Mechanick JI, Bergman DA, Braithwaite SS, Palumbo PJ.American Association of Clinical Endocrinologists protocol for standardized production of clinical practice guidelines [published correction appears in EndocrPract. 2008;14:802-803]. EndocrPract. 2004; 10:353-361.

10. Mestron A, Webb SM, Astorga R, et al. Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (RegistroEspanol de Acromegalia, REA). Eur J Endocrinol. 2004; 151:439-446.

11. Rivoal O, Brézin AP, Feldman-Billard S, Luton JP. Goldmannperimetry in acromegaly: a survey of 307 cases from 1951 through 1996. Ophthalmology. 2000; 107:991-

997.
12. Melmed S. Medical progress: acromegaly [published correction appears in N Engl J Med. 2007; 356:879]. N Engl J Med. 2006; 355:2558-2573.
13. Brabant G, von zurMühlen A, Wüster C, et al. Serum insulin-like growth factor I reference values for an automated chemiluminescence immunoassay system: results from a multicenter study. Horm Res. 2003; 60:53-60. [EL 1]
14. Melmed S. Confusion in clinical laboratory GH and IGF-I reports. Pituitary. 1999; 2:171-172.
15. Freda PU, Post KD, Powell JS, Wardlaw SL. Evaluation of disease status with sensitive measures of growth hormone secretion in 60 postoperative patients with acromegaly. J ClinEndocrinolMetab. 1998; 83:3808-3816.
16. Giustina A, Chanson P, Bronstein MD, et al (Acromegaly Consensus Group). A consensus on criteria for cure of acromegaly. J ClinEndocrinolMetab. 2010; 95:31413148.
17. Ezzat S, Forster MJ, Berchtold P, Redelmeier DA, Boerlin V, Harris AG. Acromegaly: clinical and biochemical features in 500 patients. Medicine (Baltimore). 1994; 73:233-240.
18. Molitch ME. Clinical manifestations of acromegaly. EndocrinolMetabClin North Am. 1992; 21:597-614.
19. Nabarro JD. Acromegaly. ClinEndocrinol (Oxf). 1987; 26:481-512.
20. Swearingen B, Barker FG II, Katznelson L, et al. Long term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J ClinEndocrinolMetab. 1998; 83:3419-3426.
21. Jadresic A, Banks LM, Child DF, et al. The acromegaly syndrome: relation between clinical features, growth hormone values and radiological characteristics of the pituitary tumours. Q J Med. 1982; 51:189-204.
22. Colao A, Pivonello R, Scarpa R, Vallone G, Ruosi C, Lombardi G. The acromegalicarthropathy. J Endocrinol Invest. 2005; 28(8 suppl):24-31.
23. Lacks S, Jacobs RP.
Acromegalicarthropathy: a reversible rheumatic disease. J Rheumatol. 1986; 13:634-636.
24. Biermasz NR, Pereira AM, Smit JW, Romijn JA, Roelfsema F. Morbidity after long-term remission for acromegaly: persisting joint-related complaints cause reduced quality of life. J ClinEndocrinolMetab. 2005; 90:27312739.
25. Biering H, Knappe G, Gerl H, Lochs H. Prevalence of diabetes in acromegaly and Cushing syndrome [in German]. Acta Med Austriaca. 2000; 27:27-31.
26. Kasayama S, Otsuki M, Takagi M, et al. Impaired betacell function in the presence of reduced insulin sensitivity determines glucose tolerance status in acromegalic patients. ClinEndocrinol (Oxf). 2000; 52:549-555.
27. Lombardi G, Galdiero M, Auriemma RS, Pivonello R, Colao A. Acromegaly and the cardiovascular system. Neuroendocrinology. 2006; 83:211-217.
28. Kraatz C, Benker G, Weber F, Lüdecke D, Hirche H, Reinwein D. Acromegaly and hypertension: prevalence and relationship to the renin-angiotensin-aldosterone system. KlinWochenschr. 1990; 68:583-587.
29. Otsuki M, Kasayama S, Yamamoto H, et al. Characterization of premature atherosclerosis of carotid arteries in acromegalic patients. ClinEndocrinol (Oxf). 2001; 54:791-796.
30. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev. 2004; 25:102-152.
31. Vitale G, Pivonello R, Galderisi M, et al. Cardiovascular complications in acromegaly: methods of assessment. Pituitary. 2001; 4:251-257.
32. Jane JA Jr, Thapar K, Laws ER Jr. Acromegaly: historical perspectives and current therapy. J Neurooncol. 2001; 54:129-137.
33. Atkinson JL, Nippoldt TB. Pituitary neurologic surgery: a unique subspecialty in evolution. EndocrPract. 2002; 8:356-361.
34. Ahmed S, Elsheikh M, Stratton IM, Page RC, Adams CB, Wass JA. Outcome of transsphenoidal surgery for acromegaly and its relationship to surgical experience. ClinEndocrinol (Oxf). 1999; 50:561-567.
35. Kreutzer J, Vance ML, Lopes MB, Laws ER Jr. Surgical management of GH-secreting pituitary adenomas: an outcome study using modern remission criteria. J ClinEndocrinolMetab. 2001; 86:4072-4077.
36. Minniti G, Jaffrain-Rea ML, Esposito V, Santoro A, Tamburrano G, Cantore G. Evolving criteria for postoperative biochemical remission of acromegaly: can we achieve a definitive cure? An audit of surgical results on a large series and a review of the literature. EndocrRelat Cancer. 2003; 10:611-619.
37. Davis DH, Laws ER Jr, Ilstrup DM, et al. Results of surgical treatment for growth hormone-secreting pituitary adenomas. J Neurosurg. 1993; 79:70-75.
38. Petrossians P, Borges-Martins L, Espinoza C, et al. Gross total resection or debulking of pituitary adenomas improves hormonal control of acromegaly by somatostatinanalogs. Eur J Endocrinol. 2005; 152:61-66.
39. Shimon I, Cohen ZR, Ram Z, Hadani M. Transsphenoidal surgery for acromegaly: endocrinological follow-up of 98 patients. Neurosurgery. 2001; 48:12391245.
40. Katznelson L. Drug insight: primary medical therapy of acromegaly. Nat ClinPractEndocrinolMetab. 2006; 2:109-117.
41. Cozzi R, Montini M, Attanasio R, et al. Primary treatment of acromegaly with octreotide LAR: a long-term (up to nine years) prospective study of its efficacy in the control of disease activity and tumor shrinkage. J ClinEndocrinolMetab. 2006; 91:1397-1403.
42. Colao A, Pivonello R, Auriemma RS, Briganti F, Galdiero M, Tortora F et al. Predictors of tumor shrinkage after primary therapy with somatostatinanalogs in acromegaly: a prospective study in 99 patients. J ClinEndocrinolMetab 2006; 91(6): 2112–2218
43. Yetkin DO, Boysan SN, Tiryakioglu O, Yalin AS, Kadioglu P. Forty month follow-up of persistent and difficultly controlled acromegalic patients treated with depot long acting somatostatinanalogoctreotide. Endocr J. 2007; 54:459-464.
44. Colao A, Ferone D, Lastoria S, et al. Prediction of efficacy of octreotide therapy in patients with acromegaly. J ClinEndocrinolMetab. 1996;81: 2356-2362.