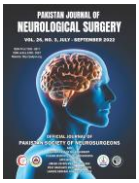

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Original Article

Outcomes of Acromegaly Patients Treated with Sandostatin LAR after Surgical Excision of Pituitary Adenoma

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ABSTRACT

Objectives: An observational study to evaluate the outcomes of Acromegaly patients treated in the department of Neurosurgery III, Punjab Institute of Neurosciences (PINS), Lahore, Pakistan.

Materials and Methods: This study was the analysis of a case series of 20 patients (mean age: 30 years) of both genders with acromegaly due to macroadenoma who had endonasal excision and postoperative treatment with Sandostatin LAR.

Results: This study consisted of a total of 20 patients out of which 11 (55%) were male and 9 (45%) were female. All 20 Patients (100%) had a headache as their main symptom and 13 patients (65%) had visual field deterioration. 19 patients (95%) had complete resection of the tumor whereas 1 (5%) had a subtotal resection. After surgery and treatment growth hormone levels improved in 19 patients (95%) and remained elevated in 1 patient (5%), IGF-1 (Insulin-like growth factor – 1) levels improved in all 20 (100%) patients. Following consecutive octreotide injections vision of 11 patients (84%) out of 13 improved and in 2 (16%) patients, it remained the same as of Preoperative status whereas Headache improved in all 20 (100%) of the patients. None of the patients had any complications related to the procedure or the injection of octreotide LAR.

Conclusion: Acromegaly due to macroadenoma responds well to treatment with octreotide LAR after endonasal resection in terms of hormonal levels and symptoms of the patients. It is a safe treatment with very less side effects and complications.

Keywords: Acromegaly, Macroadenoma, Growth Hormone, Insulin-like growth factor – 1.

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INTRODUCTION

About 15% of primary intracranial neoplasms are pituitary tumors.[1] Hormonal signals that regulate thyroid, reproductive, growth, and metabolic processes are integrated by the pituitary gland. In response to the hypothalamus, intra-pituitary,

and peripheral hormonal and growth factor signals, several cellular compartments inside the pituitary gland release highly specialized trophic hormones. When some types of pituitary cells multiply and oversecrete their respective hormones, benign monoclonal adenomas can form.[2] Acromegaly is a slowly progressing condition brought on by increased production of growth hormone (GH) and, as a result, insulin-like growth factor-I (IGF1). In most cases, a GH-secreting pituitary tumor causes this, but it can also occasionally be brought on by pituitary hyperplasia, ectopic GH, or GH-releasing hormone (GHRH) secretion.[3] The most typical symptoms of acromegaly are facial and acral dysmorphia, which includes big hands and feet, broad, stubby fingers, and thickened soft tissues. Acromegaly patients have a distinctive physical profile, including a rectangular face, an expanded, broadened nose, pronounced cheekbones, a bulging forehead, thickened lips, and noticeable skin wrinkles. Prognathism, maxillary broadening, tooth separation, and malocclusion of the jaw are common (misalignment of the teeth). Acromegaly is associated with non-specific symptoms like headache, asthenia, hyperhidrosis, acroparaesthesia, and joint pain in addition to enlargement of the limbs and facial features.[4] According to studies from the 1980s and 1990s, there are 0.28 to 0.4 occurrences of acromegaly per 100,000 people year worldwide.[5] In contrast, more recent investigations have found a substantially higher global yearly incidence of up to 1.1 cases per 100,000 people.[6] Although a few research revealed a slightly higher prevalence of acromegaly in males than in women, the majority of investigations found no difference in prevalence between the sexes.[7] Patients may have concomitant conditions such as diabetes or glucose intolerance, hypertension, OSAS, cardiomyopathy (mostly left ventricular hypertrophy), and goiter when they are diagnosed.[3] To reduce mortality, acromegaly treatment tries to normalize GH and IGF1 levels, limit tumor bulk, and lower the chance of developing systemic comorbidities.[9] The majority of patients currently receive their first-line care for acromegaly through transsphenoidal neurosurgery, which allows for the selective removal of the pituitary adenoma. From reviews recently.[10] The majority of acromegalics receive treatment with the long-acting somatostatin analog octreotide (OCT), which lowers GH levels. Currently, this method cannot be recommended as a first-line treatment because most patients experience a relapse of their sickness after stopping their medication.[11] The responsiveness to treatment is noticeably better in patients treated with octreotide (Sandostatin LAR) following surgical debulking or total excision than in those treated with primary medicinal treatment or even with simply surgical treatment.[12] Direct costs for the management of acromegaly have a significant burden on the healthcare systems. while follow-up length represented a major determinant of biochemical outcome.[13] The rationale of this study was to observe whether Acromegaly due to macroadenoma responds well to treatment with octreotide LAR after endonasal resection in terms of hormonal levels and symptoms of the patients, the safety of treatment, its side effects, and complications.

MATERIALS AND METHODS

Study Design

This is the observational study comprised of case series of 20 patients diagnosed with Acromegaly due to Growth hormone-producing pituitary macroadenoma who underwent transsphenoidal endonasal excision and got Sandostatin LAR 20 mg for 1 year (June 2021 to June 2022) at the Neurosurgery unit 3, Punjab Institute of Neurosciences, Lahore.

Inclusion Criteria

All the patients of both genders and all age

groups admitted in Neurosurgery Unit 3, Punjab Institute of Neurosciences, Lahore, with the clinical diagnosis of acromegaly, with raised Serum growth hormone levels that were not improving after oral glucose tolerance test, raised IGF-1 levels and were having pituitary macroadenoma on MRI with the pituitary protocol from June 2021 to June 2022, who had endonasal transsphenoidal excision of adenoma and got Injection Sandostatin LAR 20mg every 30 days.

Exclusion Criteria

Patients who had transcranial excision, those who couldn't get Injection Sandostatin LAR, or those who were lost to follow-up.

Data Collection and Clinical Management

Between June 2021 and June 2022, 20 patients with Acromegaly due to pituitary macroadenoma (11 men and 9 women) with a mean age of 30 years had endonasal transsphenoidal excision followed by Intramuscular injection of Sandostatin LAR 20 mg after every 30 days interval at Punjab Institute of Neurosciences Unit 3. Headache evaluated with VAS score, Visual field assessed using digital perimetry pre-operative and at every 6 months follow up. Recurrence and post-operative problems were also assessed. All patients underwent pre-operative imaging, which comprised Ct brain plain, MRI brain using a pituitary protocol, and pictures with axial, coronal, and sagittal cuts in T1 and T2-weighted images. Biochemical testing included pre-operative Serum Growth hormone levels, S/IGF-1 levels, pituitary hormonal profile (serum cortisol, S/TSH, and S/Prolactin levels), Immediate postoperative S/Growth hormone level with oral glucose tolerance test, S/IGF levels after 1 month and then S/IGF levels after every 3 months. The extent of resection was assessed through an MRI brain with IV contrast after 1 month of surgery, Incomplete resection/Residual tumor is defined as a tumor visible on the MRI. Evaluation of improvement in Signs/symptoms and biochemical tests was assessed during 1 monthly outpatient session. Recurrence of adenoma was monitored with an MRI brain with contrast after every 6 months. A limited no of patients was included in this study due to loss of follow-up and long-term affordability issues. All patient's data was used after their consent.

RESULTS

Age and Gender Distribution

A total of 20 patients participated in the study, ranging in age from 21 to 45 and with a mean age of 30. Male patients make up 11 (55%) of the total patients, while female patients make up 9 (45%).

Signs and Symptoms

Out of a total of 20 patients, visual field defects were present in 13 Patients (65%) and 7 patients (35%) had a normal visual field. All 20 patients (100%) included in the study had a headache as one of the primary symptoms (Table 1).

Table 1: Signs and symptoms.

Major Signs and Symptoms:	No. of Patients	Percentages
Headache:	20	100%
Visual field deterioration	13	65%

Immediate Postoperative Growth Hormone Levels

Post-operative growth hormone levels improved after surgery in 19 patients (95%) whereas in 1 patient (5%) it didn't improve (Table 2).

Table 2: Immediate Postoperative Growth Hormone levels.

Growth Hormone Levels:	No. of Patients	Percentages
Improved	19	95%
Not Improved	1	5%

Improvement in S/IGF-1 Levels

Over 6 months after surgery, S/IGF-1 levels improved in all 20 patients (100%) (Table 3).

Table 3: Improvement in S/IGF-1 Levels.

Serum IGF level (Improvement Over 6 Months Period)	No. of Patients	Percentages
Improved	20	100%
Not Improved	0	0

Improvement in Visual Field Defects

Visual Field deterioration was present in 13 patients preoperatively out of these 11 patients (84%) had significant improvement in their visual field defects whereas in 2 patients visual field defects remained the same (Table 4).

Table 4: Improvement in Visual field defects.

Visual Improvement (After 6 months of Surgery and Octreotide LAR Inj. out of 7 patients)	No. of Patients	Percentages
Improved	11	84%
Not improved	2	16%

Improvement in Headache

After 6 months of surgery, all 20 (100%) patients showed significant improvement in headache (Table 5).

Residual Tumor

Residual tumor was left in 1 patient (9%), and in 10 patients (91%) complete resection of the tumor was achieved (Table 6).

Table 5: Improvement in Headache.

Headache:	No. of patients	No. of Patients
Improved	11	100%
Not improved	0	0

Table 6: Residual Tumor.

Residual Tumor:	No. of Patients	Percentages
Residual Tumor	1	10%
Complete Resection	10	90%

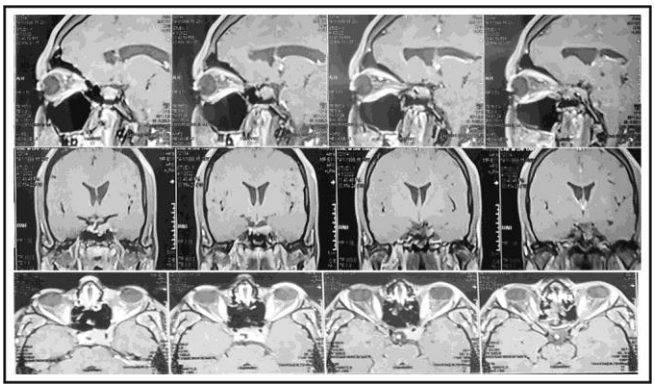

Fig. 1 (A): Pre-op MRI Brain.

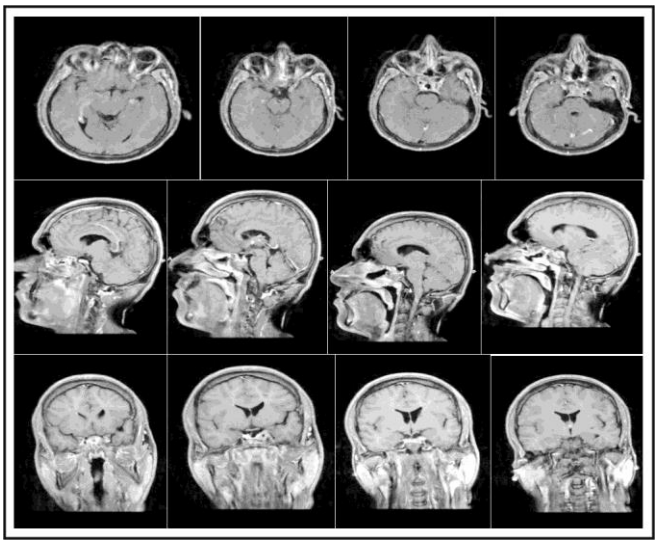

Fig. 1 (B): Post-op MRI Brain (Images used with permission).

DISCUSSION

Due to their excellent risk/benefit profiles, lanreotide and octreotide LAR are utilized as first-

line treatments. On long-term treatment with these, 30 to 55% of patients reach normal IGF-I, and more than half of treated patients experience tumor size reductions of at least 20%.[15] Age and lower baseline IGF-I levels are excellent predictors of response.[16] Patients who are insufficiently managed on regular doses but responsive to SRL therapy may benefit from increasing the dose and/or frequency of octreotide LAR and lanreotide.[17] The use of an oral formulation of octreotide as a long-term maintenance therapy for patients who have responded to and tolerated treatment with octreotide or lanreotide was recently approved in the United States.[18] In certain patients whose IGF-1 levels were not sufficiently controlled by octreotide LAR or lanreotide,[19] pasireotide LAR can be beneficial. It may also result in a better rate of tumor shrinking.[20] Gallstones and GI problems are the main side effects of SRL.[21] Although some people experience minor hyperglycemia, long-term octreotide LAR and lanreotide typically have no overall negative effects on how the body processes glucose.[22] Pasireotide LAR, in comparison, results in hyperglycemia in up to 70% of patients, including secondary diabetes in 25% to 40% of patients.[23] Therefore, candidates for pasireotide LAR should undergo rigorous screening and glycemic side effect monitoring. There are no controlled trials on the best way to treat pasireotide-induced hyperglycemia. Glucagon-l may be more effective in managing patients whose oral antidiabetic drugs, including metformin, are failing to regulate their blood sugar levels.

The results of this study show that after surgical excision and medical management with Sandostatin LAR post-surgically there is a significant improvement in both symptoms and biochemical markers of acromegalic patients **(Table 3, 4, 5)**. In this 1-year study of 20 patients, all of them were treated with surgical debulking/ excision via endonasal transsphenoidal approach and then medically treated with Sandostatin LAR 20mg IM injection until the Growth Hormone levels became less than 2.5ng/ml during OGTT and normal age and sex-adjusted S/IGF-1 levels achieved. The patients presented with a wide variety of signs and symptoms, where the headache was present in all 20 patients and visual field deterioration was in 13 patients, all of them had raised Growth hormone and S/IGF-1 levels, and on MRI there was pituitary macroadenoma. Post-operative growth hormone levels improved after surgery in 19 patients (95%) whereas in 1 patient (5%) it didn't improve (Table 2). Over 6 months after surgery, S/IGF-1 levels improved in all 20 patients (100%) (Table 3). Visual Field deterioration was present in 13 patients preoperatively out of these 11 patients (84%) had significant improvement in their visual field defects whereas in 2 patients visual field defects remained the same (Table 4). After 6 months of surgery, all 20 (100%) patients showed significant improvement in headache (Table 5). In the literature overall improvement in biochemical markers of patients treated with surgical debulking are 57.3% of 688 patients[24] and 61% of 100 patients[25] whereas, in patients who had only medical management with Sandostatin LAR, the suppression of Growth hormone and IGF-1 was 50%[(26)] though the improvement in signs and symptoms is significant when treated with Sandostatin even when IGF-1 Levels are not improved.[27] In this study both of the treatment modalities were used to treat the patients, Outcomes showed that growth hormone levels with OGTT improved in 95% of the patients after surgery whereas IGF-1 levels improved in 100% of the patients during 1 year with medical treatment after surgery. In terms of signs and symptoms after treatment headaches got resolved in 100% whereas visual field defect improved in 86% of the patients. In 95% of the patients there was complete surgical removal of the tumor and in 5% the resection was partial.

STRENGTHS

In Pakistan, less literature is present on the outcomes of Acromegaly patients treated with Sandostatin LAR after surgical excision of pituitary adenoma. This could act as an initiative for further research in this area. Our results suggest that after maximum debulking of the tumor, the medical treatment provides significant improvement and can lead to a definitive cure of the disease in terms of biochemical markers and relief of major symptoms and signs.

LIMITATIONS

The sample size was small due to which the results can't be generalized. It was an observational research design due to which no causative decisions could be made with certainty. There was a loss of follow-up due to cost-effectiveness for long-term postoperative medical therapy.

FUTURE RECOMMENDATION

This study has laid the basis for future studies in Pakistan. It is recommended that in future studies, a longitudinal research study is used to see the long-term effects and differences in the outcome of Acromegaly patients treated with Sandostatin LAR after surgical excision of pituitary adenoma.

CONCLUSION

In conclusion, the first line treatment of acromegaly due to Growth hormone-secreting pituitary adenoma is surgery via an endonasal transsphenoidal approach. Medical treatment with Sandostatin LAR is effective but it's not definitive. Implying both the treatments individually GH levels and S/IGF-1 levels may remain raised and clinical signs/symptoms might continue to persist. This study shows that the best approach is to use both modalities together. After maximum debulking of the tumor, the medical treatment provides significant improvement and can lead to a definitive cure of the disease in terms of biochemical markers and relief of major symptoms and signs.

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Additional Information

Disclosures: Authors report no conflict of interest.
Ethical Review Board Approval: The study was conformed to the ethical review board requirements.
Human Subjects: Consent was obtained by all patients/participants in this study.
Conflicts of Interest:
In compliance with the ICMJE uniform disclosure form, all authors declare the following:
Financial Relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.
Other Relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR CONTRIBUTIONS

Sr. No.	Author's Full Name	Intellectual Contribution to Paper in Terms of
1.	Sumira Kiran	Study Design, Methodology, and Paper Writing.
2.	Muhammad Kaleem Iftikhar	Data Calculation and Data Analysis.
3.	Muhammad Naveed Majeed	Interpretation of Results.
4.	Ch. Arslan Ahmad	Statistical Analysis.
5.	Khawar Anwar	Literature Review.
6.	Asif Bashir	Literature Review and Quality Insurer.