RESEARCH ARTICLE

Diagnostic characteristics and management outcome in patients with acromegaly: A 15-year experience at a tertiary care hospital in Pakistan

Shehla Tabassum, Sajjad Ali khan, Nanik Ram, Najmul Islam

Abstract

Objective: To assess the diagnostic features of acromegaly, and analyse its management outcomes over a 15-year period in a tertiary care setting.

Method: The descriptive, cohort, retrospective study was conducted at the Aga Khan University Hospital, Karachi, and comprised data of adult patients of either gender diagnosed with acromegaly based on biochemical and radiological evidence between January 2005 and December 2019. Data was retrieved from the medical records. Data was analysed using SPSS 19.

Results: Of the 84 subjects, 54(64.3%) were males and 30(35.7%) were female. The overall mean age was 38.69±13.52 years. The patients presented 5.43±4.3 years after the onset of symptoms, with somatic growth features, such as enlarged hands and feet which was the most common complaint 81(96.4%). Of all the patients, 73(86.9%) underwent trans-sphenoidal surgery for the removal of the pituitary adenoma, while 11(13.1%) opted out of the surgical option. Further, 9(12.3%) patients showed biochemical and radiological remission 6 months post-surgery. Out of the remaining 64(87.7%) patients, 38(59.4%) received radiosurgery or radiotherapy, 15(23.4%) underwent repeat trans-sphenoidal surgery, and 11(17.2%) chose medical treatment.

Conclusion: Majority of patients failed to achieve remission after trans-sphenoidal surgery, which is the first line of treatment. Radiotherapy/repeat surgery was generally the options taken by those with persistent disease.

Keywords: Acromegaly, Characteristics, Diagnosis, Management, Outcome, Pituitary tumour, Growth hormone.

(JPMA 74: 1041; 2024) **DOI: https://doi.org/10.47391/JPMA.8604**

Introduction

Acromegaly is caused by excess growth hormone (GH) production, usually as a result of pituitary adenoma.[1] Over 70% of somatotroph adenomas are macroadenomas at diagnosis with extension into sellar or suprasellar areas.[2]

In Pakistan, the prevalence is reported to be 17.6% among pituitary macroadenomas >10mm and 14% among microadenomas <10mm.[3] It is a rare condition with an incidence of 3-11 new cases per million of population per year. The diagnosis is often preceded by around 5-10 years of active, but unrecognised disease.[4] Clinical expression of the disease in each patient depends on the levels of GH and insulin-like growth factor-1 (IGF-1), as well as age, tumour size, and the delay in diagnosis.[5]

The typical features include signs of somatic overgrowth, including soft tissue swelling, enlarged hands and feet, and protrusion of lower jaw called prognathism. The growth of pituitary adenoma may compress local structures and cause neurological symptomatology, headache and visual disturbances. Other features include sleep apnoea, arthralgia to arthritis, vertebral fractures, hypogonadism, and colonic polyps.[6] Acromegaly is associated with cardiovascular complications, including hypertension (HTN), stroke, arrhythmias, valvular lesions and diastolic dysfunction. Furthermore, acromegaly is also associated with insulin resistance, leading to overt diabetes mellitus (DM) and prediabetes.[7]

Acromegaly is biochemically diagnosed by failure to suppress GH to <1µg/L after oral glucose tolerance test (OGTT), and elevated IGF-1 for age, and radiologically by magnetice resonance imaging (MRI) with contrast enhancement.[8]

Trans-sphenoidal surgery (TSS) is the treatment of choice in acromegaly. Medical treatment in the form of dopamine agonists, somatostatin analogues and GH receptor antagonists are usually indicated after unsuccessful TSS and while awaiting the effects of radiotherapy. Remission after TSS is defined as random GH <1ng/ml and age-normalized IGF-1 levels at least 6 months post-surgery.[9]

This important, although rare endocrine entity of acromegaly, needs to be studied in Pakistan as regional data on acromegaly is scarce. The current study was planned to fill the gap by assessing the diagnostic features of acromegaly, and analysing its management outcomes over a 15-year period in a tertiary care setting.

Aga Khan University Hospital, Karachi, Pakistan.

Correspondence: Nanik Ram. e-mail: nanikkhatwani@yahoo.com

ORCID ID. 0000-0002-2447-2630

Submission complete: 28-12-2022 **Review began:** 14-03-2023

Acceptance: 06-03-2024 **Review end:** 02-03-2024

Materials and Methods

Method: The descriptive, cohort, retrospective study was conducted at the Aga Khan University Hospital, Karachi, and comprised patient data between January 2005 and December 2019. As the study was retrospective, the research protocol was reviewed by the institutional ethics review committee, and the requirement of informed consent was deemed exempted. All patients at the AKUH are informed at the time of their visit that their health information may be used for research purposes. The data collected did not include personal identifiers, and access to the medical records was obtained through the Medical Record Room personnel, without the need for additional permission.

The sample was raised using convenience sampling technique, and data of all individuals diagnosed with acromegaly who visited the study location between the targeted 15-year period was reviewed in 2020-21. Those included were adult patients of either gender diagnosed with acromegaly based on biochemical and radiological evidence, and had post-surgical 6-month record of GH and/or IGF-1 levels if they underwent TSS. Data of patients with tumours that secrete both GH and prolactin was excluded.

Patient's medical record files were reviewed. Inpatient and outpatient records were included. Demographic, clinical and laboratory data, information related to treatment patterns, and follow-up notes for acromegaly were all used.

Data was analysed using SPSS 19. Descriptive analysis was carried out for all variables. Data was expressed as mean ± standard deviation, or as frequencies and percentages, as appropriate. After checking data normality, comparison was done using appropriate statistical tests, including chi-square and t-tests. $P<0.05$ was considered significant.

Results

Of the 84 subjects, 54(64.3%) were males and 30(35.7%) were female. The overall mean age was 38.69±13.52 years. The patients presented 5.43±4.3 years after the onset of symptoms, with somatic growth features, such as enlarged hands and feet which was the most common complaint 81(96.4%). Visual disturbance was present in 21(25%) patients (Table 1).

Patients in remission were relatively younger with shorter duration of the disease, and most symptoms and signs were much less prevalent in patients with remission compared to those without remission (Table 2).

Of all the patients, 73(86.9%) underwent TSS for the removal of the pituitary adenoma, while 11(13.1%) opted out of the surgical option. Further, 9(12.3%) patients showed biochemical and radiological remission 6 months post-surgery. Out of the remaining 64(87.7%) patients, 38(59.4%) received radiosurgery or radiotherapy, 15(23.4%) underwent repeat TSS, and 11(17.2%) chose medical treatment. The factors affecting remission after TSS in acromegaly were large tumour size, high IGF-1 level and tumour compression over optic chiasma (Table3).

Table-1: Demographic and clinical characteristics (n=84).

	Total (n=84) n (%) Mean±SD	**Male** (n=54) n (%) Mean±SD	**Female** (n=30) n (%) Mean±SD
Age at time of diagnosis (year)	38.69±13.52	37.09±13.85	41.57±12.62
Duration of symptoms (year)	5.43±4.3	4.69±3.56	6.77±5.19
Somatic growth features	81 (96.4)	54 (100)	27(90)
Pre-surgery GH (n=73)	47.88±51.83	-	-
Pre-surgery IGF-1 (n=73)	838.39±321.00	-	-
Suppressed other pituitary hormone	27 (32.1)	15 (27.8)	12 (40)
Post-surgery GH (n=73)	25.92±47.69	-	-
Post-surgery IGF-1 (n=73)	561.45±296.16	-	-
Macroadenoma	73 (86.9)	45 (83.3)	28 (93.3)
Microadenoma	11 (13.1)	9 (16.7)	2 (6.7)
Optic chiasm compression	26(31)	14 (25.9)	12 (40)
Remission achieved after initial treatment (n=84)	10 (11.9)	6 (11.1)	4 (13.3)
Remission achieved after surgery (n=73)	9 (12.3)		
Modality used for initial disease:			
Medical	11 (73)	7 (47)	4 (26)
Surgery	13 (86.9)	13 (87)	13.3 (86.7)
Modality used for persistent disease (n=74):			
Medical	19 (25.6)-	-	-
Radiotherapy	39 (52.7)-	-	-
Repeat Surgery	16 (21.6)	-	-

SD: Standard deviation, GH: Growth hormone, IGF-1: Insulin-like growth factor-1.

Table-2: Factors affecting remission after TSS in acromegaly.

	In Remission (n=10) n (%) Mean±SD	**Without Remission** (n=74) n (%) Mean±SD
Age at time of diagnosis (year)	35.7±9.47	39.09±14
Male	6 (60)	48 (64.9)
Female	4 (40.0)	26 (35.1)
Duration of symptoms (year)	3.42±2.77	5.7±4.41
Pre-treatment GH	20.85± 9.48	49.7±52.2
Pre-treatment IGF-1	720.2±259.47	833.1±318.5
Suppressed other pituitary hormone	2 (20.0)	25 (33.8)
Macroadenoma	7 (70.0)	66 (89.2)
Microadenoma	3 (30.0)	8 (10.8)
Optic chiasm compression	2 (20.0)	24 (32.4)
Modality used for initial disease:		
Medical	1(10)	64(86.5)
Surgery	9 (90)	10 (13.5)

SD: Standard deviation, GH: Growth hormone, IGF-1: Insulin-like growth factor-1.

Table-3: Factors affecting remission after TSS in acromegaly.

	In Remission (n=9) n (%)	Without Remission (n=64) n (%)	*p*-value
Age at time of diagnosis (year)	36.6±9.6	37.7±13.06	0.709
Male	6 (66.7)	41 (64.1)	<0.001
Female	3 (33.3)	23 (35.9)	<0.001
Duration of symptoms (year)	3.7±2.8	5.46±4.4	0.300
Pre-treatment GH	20.28±9.88	51.75±54.16	0.701
Pre-treatment IGF-1	695.44±259.43	858.49±325.40	0.535
Suppressed other pituitary hormone	2 (22.2)	24 (37.5)	<0.001
Post-treatment GH	0.58±0.36	29.49±49.96	0.414
Post-treatment IGF-1	189.7±54.37	613.73 ± 278.1	0.414
Macroadenoma	6 (66.7)	59 (92.2)	<0.001
Microadenoma	3 (33.3)	5 (7.8)	<0.001
Optic chiasm compression	2 (22.2)	23 (35.9)	<0.001

TSS: Trans-sphenoidal surgery, GH: Growth hormone, IGF-1: Insulin-like growth factor-1.

Discussion

The current findings revealed that there was a higher incidence of acromegaly among males than females. This was in contrast to previous studies that reported a higher prevalence of acromegaly in women.[10-12]

The findings showed that the mean age at diagnosis was 39.68±14.36 years, with females experiencing a slightly later onset than males (43.25 vs 37.52 years). The findings were not consistent with earlier studies that reported mean age of >45 years.[10-12]

Acromegaly is distinguished by progressive and consistent bodily changes, including increased size of facial features and limbs. Therefore, the detection of the disease typically takes place when a new physician examines the patient, or when older photographs are used for comparison of physical features. Research has demonstrated that there is a delay of 5-10 years between the emergence of initial symptoms and the diagnosis.[12,13] In the current study, patients reported with an average symptom duration of 5.91 years. This result is consistent with previous research done in Japan and Turkey.[13,14]

As per the current findings, alterations in facial and acral features were observed in 96.2% patients, making it the most prevalent reason for their initial presentation. Enlarged hands and feet (96.2%), a larger nose (88.7%), and prognathism (75.5%) were the most common somatic changes noticed. In addition, the study also found that the prevalence rates of headache, tiredness, increased sweating, and visual disturbance were 66%, 60.4%, 34% and 22.6%, respectively. The findings aligned with previous studies done globally[15-17] but were differ from the Liège Acromegaly Survey (LAS) database, which reported a considerably lower frequency of these symptoms.[12]

DM and HTN were found in 35.5% and 32.1% of individuals with comorbidities, respectively. The mean systolic and diastolic blood pressure measurements were 126.9±16.04 mmHg and 79.39±10.07 mmHg, respectively. The occurrence of ischaemic heart disease (IHD) and obstructive sleep apnoea (OSA) was both 3.85%. The rates for DM and HTN were in line with other studies.[10,11,18] The increased occurrence of DM was consistent with earlier findings that suggested the prevalence ranging from 22% to 40% in various populations.[10,11,19-21]

MRI is the preferred method for evaluating tumour size and invasiveness. The current study found a considerably higher prevalence of macroadenoma at 94.3%. A multicentre study in Spain documented a frequency of 73% for acromegalic patients with macroadenoma, whereas another study reported 71%.[10,22]

The higher occurrence of macroadenomas could potentially be attributed to the delayed identification of acromegaly. Nevertheless, despite the heightened frequency of macroadenomas, only 28.3% of cases exhibited indications of optic chiasm compression, which was only slightly more frequent than the prevalence of visual field defects that were observed in 20.8% of the current cases.

The primary treatment for acromegaly is surgery, which was utilised in 87% of the current patients through TSS. The remaining 13% received medical therapy as their initial treatment. This approach was in line with other studies.[10,23] Medical treatment of acromegaly includes somatostatin receptor ligands (SRLs), octreotide low anterior resection (LAR), lanreotide or pasireotide. This treatment is costly and there is no insurance or third-party coverage for most of the patients in lower middle-income countries. Thus, most patients cannot afford long-term medical treatment. Only octreotide LAR is available in Pakistan, which costs Pakistan rupees (PKR) 78,000 for a 20mg dose per month, while the single-time TSS costs around PKR 800,000.

A cure for acromegaly can be achieved by lowering circulating IGF-1 levels to a normal range for the patient's age and ensuring that nadir GH levels are <1µg/L after an oral glucose load. In the current study, the average GH level before surgery was 58.42±56.33%, and after surgery, the GH levels were only evaluated in 50 patients, showing a decrease to 27.96±35.15%. Similarly, the average IGF-1 level before surgery was 757.35±279.46, which reduced to 509.76±255.76 after surgery. These results demonstrate that the disease persisted in many cases, and surgeons had a crucial role to play in managing the illness.

Among those who had surgery as their primary treatment,

only 9(12.3%) patients showed biochemical and radiological remission 6 months post-surgery. Out of the remaining 64(87.7%) patients, 38(59.4%) received radiosurgery or radiotherapy, 15(23.4%) underwent repeat TSS, and 11(17.2%) chose medical treatment to control the disease. The percentage of patients who achieved remission after surgery in the current study was notably lower compared to the remission rates of 40.3% in the Spanish population, 43.7% in the United Arab Emirates (UAE) population, and 49% in the Belgian population.[10,24,25]

Medical treatment is generally recommended for individuals with active acromegaly. In the study, somatostatin analogues (SSAs) were given to most patients as either monotherapy or in combination with dopamine agonists.

Typically, selective adenomectomy does not affect the patient's pituitary function, and any pre-existing suppression usually improves following tumour removal. However, the current study revealed that 34% of patients had hypopituitarism before the surgery, which persisted even after the procedure.

The current study had a variety of limitations As it had a retrospective design. Moreover, some of the patients followed up with neurosurgeons instead of endocrinologists. Inaccessibility of IGF-1 level measurement was noted, and very few of the patients had dynamic testing done to assess the treatment outcome.

Conclusion

Macroadenoma was the predominant cause of acromegaly. Most commonly, it presented with somatic features and was associated with comorbidities, including DM and HTN. Surgery was the modality of choice for the management of acromegaly, and medical therapy along with radiotherapy could also be considered in selected patients with residual/active disease.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Fleseriu M, Langlois F, Lim DST, Varlamov EV, Melmed S. Acromegaly: pathogenesis, diagnosis, and management. Lancet Diab Endocrinol. 2022; 10:804-26.doi: 10.1016/S2213-8587(22)00244-3.
2. Ershadinia N, Tritos NA. Diagnosis and Treatment of Acromegaly: An Update. Mayo Clin Proceed. 2022;97:333-46. doi: 10.1016/j.mayocp.2021.11.007.
3. Ishtiaq O, Haq MU, Rizwan A, Masood MQ, Mehar S, Jabbar A. Etiology, functional status and short term outcome of patients with pituitary lesions. An experience from a developing country. J Pak Med Assoc. 2009; 59:839-43.
4. Nachtigall LB, Guarda FJ. The Clinical Presentation of Acromegaly. In: Blevins Jr LS, Aghi MK, eds. Acromegaly: A Guide to Diagnosis and Treatment. Cham: Springer International Publishing, 2022; pp-55-65.
5. Varlamov EV, Niculescu DA, Banskota S, Galoiu SA, Poiana C, Fleseriu M. Clinical features and complications of acromegaly at diagnosis are not all the same: data from two large referral centers. Endocr Connect. 2021; 10:731-41. doi: 10.1530/EC-21-0035.
6. Ahmed S, Ashraf AT, Mushtaq MJ, Haroon ZH. Clinical parameters and treatment outcome in patients of acromegaly: A retrospective analysis of 51 patients. J Pak Med Assoc. 2022; 72:346-8. doi: 10.47391/JPMA.2104.
7. Hong S, Kim KS, Han K, Park CY. Acromegaly and cardiovascular outcomes: a cohort study. Eur Heart J. 2021; 43:1491-9. doi: 10.1093/eurheartj/ehab822.
8. Akirov A, Masri-Iraqi H, Dotan I, Shimon I. The Biochemical Diagnosis of Acromegaly. J Clin Med. 2021; 10:1147. doi: 10.3390/jcm10051147.
9. Katznelson L, Laws ER, Jr, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2014; 99:3933-51. doi: 10.1210/jc.2014-2700.
10. Mestron A, Webb SM, Astorga R, Benito P, Catala M, Gaztambide S, et al. Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Espanol de Acromegalia, REA). Eur J Endocrinol. 2004; 151:439-46. doi: 10.1530/eje.0.1510439.
11. Rolla M, Jawiarczyk-Przybyłowska A, Halupczok-Żyła J, Kałużny M, Konopka BM, Błoniecka I, et al. Complications and Comorbidities of Acromegaly-Retrospective Study in Polish Center. Front Endocrinol (Lausanne). 2021; 12:642131. doi: 10.3389/fendo.2021.642131.
12. Petrossians P, Daly AF, Natchev E, Maione L, Blijdorp K, Sahnoun-Fathallah M, et al. Acromegaly at diagnosis in 3173 patients from the Liège Acromegaly Survey (LAS) Database. Endocr Relat Cancer. 2017; 24:505-18. doi: 10.1530/ERC-17-0253.
13. Fukuda I, Hizuka N, Murakami Y, Itoh E, Yasumoto K, Sata A, et al. Clinical features and therapeutic outcomes of 65 patients with acromegaly at Tokyo Women's Medical University. Intern Med. 2001; 40:987-92. doi: 10.2169/internalmedicine.40.987.
14. Evran M, Sert M, Tetiker T. Clinical experiences and success rates of acromegaly treatment: the single center results of 62 patients. BMC Endocr Disord. 2014; 14:97. doi: 10.1186/1472-6823-14-97.
15. Portocarrero-Ortiz LA, Vergara-Lopez A, Vidrio-Velazquez M, Uribe-Diaz AM, García-Dominguez A, Reza-Albarrán AA, et al. The Mexican Acromegaly Registry: Clinical and Biochemical Characteristics at Diagnosis and Therapeutic Outcomes. J Clin Endocrinol Metab. 2016; 101:3997-4004. doi: 10.1210/jc.2016-1937.
16. Al Dahmani K, Afandi B, Elhouni A, Dinwal D, Philip J, Bashier A, et al. Clinical Presentation, Treatment, and Outcome of Acromegaly in the United Arab Emirates. Oman Med J. 2020; 35:e172. doi: 10.5001/omj.2020.51.
17. Hong JW, Ku CR, Kim SH, Lee EJ. Characteristics of acromegaly in Korea with a literature review. Endocrinol Metab (Seoul). 2013; 28:164-8. doi: 10.3803/EnM.2013.28.3.164.
18. Kraatz C, Benker G, Weber F, Lüdecke D, Hirche H, Reinwein D. Acromegaly and hypertension: prevalence and relationship to the renin-angiotensin-aldosterone system. Klinische Wochenschrift. 1990; 68:583-7. doi: 10.1007/BF01660954.
19. Fieffe S, Morange I, Petrossians P, Chanson P, Rohmer V, Cortet C, et al. Diabetes in acromegaly, prevalence, risk factors, and evolution: data from the French Acromegaly Registry. Eur J Endocrinol. 2011; 164:877-84. doi: 10.1530/EJE-10-1050.

20. Alexopoulou O, Bex M, Kamenicky P, Mvoula AB, Chanson P, Maiter D. Prevalence and risk factors of impaired glucose tolerance and diabetes mellitus at diagnosis of acromegaly: a study in 148 patients. Pituitary. 2014; 17:81-9. doi: 10.1007/s11102-013-0471-7.

21. Tutuncuoğlu P, Saraç F, Saygili F, Ozgen AG, Yilmaz C, Tüzün M. Diabetes and impaired glucose tolerance prevalences in Turkish patients with impaired fasting glucose. Acta Diabetol. 2008; 45:151-6. doi: 10.1007/s00592-008-0034-y.

22. Fukuda I, Hizuka N, Murakami Y, Itoh E, Yasumoto K, Sata A, et al. Clinical features and therapeutic outcomes of 65 patients with acromegaly at Tokyo Women's Medical University. Internal Med. 2001; 40:987-92. doi: 10.2169/internalmedicine.40.987.

23. Katznelson L, Laws ER, Jr, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014; 99:3933-51. doi: 10.1210/jc.2014-2700.

24. Al Dahmani K, Afandi B, Elhouni A, Dinwal D, Philip J, Bashier A, et al. Clinical Presentation, Treatment, and Outcome of Acromegaly in the United Arab Emirates. Oman Med J. 2020; 35:e172-e. doi: 10.5001/omj.2020.114.

25. Bex M, Abs R, T'Sjoen G, Mockel J, Velkeniers B, Muermans K, et al. AcroBel – the Belgian registry on acromegaly: a survey of the 'real-life' outcome in 418 acromegalic subjects. Eur J Endocrinol. 2007; 157:399-409. doi: 10.1530/EJE-07-0358.

Author Contribution:
ST: Data collection and entry.
SAK: Data analysis.
NR: Writing.
NI: Research idea.