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Patient's point of view on the diagnosis, treatment, and follow-up in acromegaly: single-center study from a tertiary center

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SUMMARY

OBJECTIVE: We aimed to evaluate the awareness and perspectives of acromegaly patients in the diagnosis and treatment processes and to evaluate basic clinical and demographic features.

METHODS: This cross-sectional study was conducted at the Endocrinology Department of Yildirim Beyazit University between March 2019 and April 2020. A total of 58 acromegalic patients were enrolled. All patients were identified from our database and called for a clinical visit and filling the questionnaire forms.

RESULTS: A total of 58 patients were included in this study (41.4% female). The mean age of the patients was 52±10.8 years. Median year from symptom to diagnosis (min-max) was 2 (1–12). Notably, 55.2% of the patients did not graduate from high school. Of the 58 patients, 30 (51.7%) patients had knowledge about the etiology of their disease. While 12 (20.7%) patients identified their initial symptoms themselves, 75% of the patients reported their symptoms during the clinical history taken by a health care professional. The majority of patients were diagnosed by an endocrinologist (69%). Acromegaly did not affect social life but affected work life and caused early retirement. Transsphenoidal surgery was performed as primary treatment in 96.6% of the patients (n=56). In all, 46 (79.3%) patients received medical treatment with somatostatin receptor ligands (e.g., octreotide or lanreotide long-acting release [LAR]) with or without cabergoline. Overall disease control was achieved in 38 (65.5%) patients.

CONCLUSIONS: Acromegaly is usually detected incidentally by clinicians. The diagnosis of acromegaly is delayed in most patients and disease-related complications have already developed at the time of diagnosis. Therefore, increasing the awareness of the society and health care professionals will reduce both disease-related comorbidities and the economic burden on the health system.

KEYWORDS: Acromegaly. Social life. Perspectives. Questionnaire.

INTRODUCTION

Acromegaly is a rare disease with incidence of 3.3 million per year, and it affects multiple organs and systems[1]. The disease is characterized by excessive growth hormone (GH) production and elevated insulin-like growth factor 1 (IGF-1). The most common etiology is a GH-secreting benign pituitary adenoma. Prolonged exposure to the hormone causes progressive somatic disfigurements, such as enlargement of hands and feet, facial overgrowth due to prognathism, and soft-tissue enlargement. The insidious onset of the symptoms and slow progress often lead to a marked delay in diagnosis, which is reported to be between 5 and 10 years after the onset of symptoms[2-4]. Before the diagnosis, the patients are usually admitted to different specialists and receive treatment for the complications without the holistic diagnosis of acromegaly. When not diagnosed and treated properly, the mortality is increased, and the patient's quality of life (QoL) is decreased. Therefore, early diagnosis of acromegaly is crucial and leads to better outcomes, including reducing overall mortality risk[5]. Timely diagnosis also enables earlier intervention for the comorbidities associated with acromegaly, consequently preventing progression to more advanced disease.

Acromegaly has several adverse effects on QoL, mostly due to musculoskeletal complications, persistent comorbidities, and economic burden of disease. Although previous studies have shown that effective and curative treatment in acromegaly significantly improves QoL, biochemical control does not correlate with clinical well-being and QoL impairments in patients who cannot achieve remission[6,7].

Since acromegaly is a rare disease, the data in the literature about the diagnostic process are scarce. In this study, our aim was to demonstrate the patients' perspective of the disease at the time of diagnosis and during the treatment. We also aimed to determine the demographic characteristics, associated comorbid conditions, and the therapeutic process in our patient group.

METHODS

This study was conducted at the Endocrinology Department of Yildirim Beyazit University between March 2019 and April

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2020. A total of 58 patients were enrolled. Before the start of the study, we obtained the local ethical board approval in accordance with principles of the Declaration of Helsinki. All patients were either operated and had histopathology proven or biochemically proven acromegaly. The patients were identified from our database and called for a clinical visit and filling the questionnaire forms. Inclusion criteria were age above 18 years at the time of enrollment, ability to understand and complete the self-reporting questionnaire, and absence of any psychiatric disorder.

The survey was created by the authors participating in the study and performed by a health care professional. The questionnaire was composed of data on the demographic features such as the age, sex, marital status, occupation, and education level. Height, weight, smoking history, diagnostic process such as the specialty and the number of clinicians that the patient visited after the onset of symptoms, reported complaints at the time of diagnosis, duration of the diagnostic process, received treatment modalities, acromegaly-related complications and accompanying comorbid conditions, and follow-up results were also included in the survey.

Statistics

For statistical analysis, SPSS version 22.0 (Statistical Package of the Social Sciences, IBM, Armonk, NY, USA) for Windows was used. Interval-scaled data were described as means and standard deviations (SD), and categorical data were described as percentage. Data were tested for normal distribution by a Shapiro-Wilk test. Free-text answers were categorized and counted. Missing variables were regarded as missing at random. Descriptive analysis was made and given as number of patients and percentage for the categorical variables. For group comparisons, unpaired t-tests or Mann-Whitney U tests for unpaired variables were used. Nominal data were calculated as valid percentage and analyzed by chi-square test or Fisher's exact test.

RESULTS

Patient characteristics

A total of 58 patients were enrolled in the study and filled out the forms. Of these, 34 (58.6%) were male and 24 (41.4%) were female. The mean age of the patients was 52±10.8 years. The oldest patient aged 72 years and the youngest one aged 25 years. Regarding educational level, 28 (48.3%) patients were graduated from primary school, 4 (6.9%) were secondary, 16 (27.6%) were high school, and 10 (17.2%) were university graduates. Out of 58 patients, 50 (86.2%) were married and 8 (13.8%) were either single or widow. Three female patients divorced after the diagnosis, and two declared the disease as the cause of divorce. Regarding occupation, 24 (41.4%) patients were retired, 14 (24.1%) were actively working, and 20 (34.5%) did not have any occupation. Also, 12 (20.7%) patients were active smoker and 46 (79.3%) patients were either non-smoker or ex-smoker. The mean height of the patients was 168±10.6 cm, and mean weight was 88.07±13.34 kg. Of the 58 patients, 22 were obese, 28 were overweight, and 8 were normal according to body mass index (BMI). The demographic features are listed in Table 1.

Table 1. Patient variables regarding the demographic features and diagnostic process.

Sex (female/male)	34 (58.6%)/24 (41.4%)
Age (years)	52±10.8
Education level	
Primary school	28 (48.3%)
Secondary school	4 (6.9%)
High school	16 (27.6%)
University	10 (17.2%)
Occupation	
Actively working	14 (24.1%)
Not working	20 (34.5%)
Retired	24 (41.4%)
Smoking status	
Smoker	12 (20.7%)
Non/ex-smoker	46 (79.3)
Height (cm)	168±10.6
Weight (kg)	88.07±13.34
BMI	
Normal	8 (13.7%)
Overweight	28 (48.2%)
Obese	22 (38.1%)
Knowledge of disease etiology (yes/no)	30 (51.7%)/28 (48.3%)
Any close relative or friend who has acromegaly (yes/no)	0 (0%)/58(100%)
Median years from symptom to diagnosis (min-max)	2 (1–12)
Symptoms noticed by	
Self	12 (20.7%)
Relative/friend	4 (6.9%)
Health care professional	42 (72.4%)

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Table 1. Continuation.

The diagnosis of acromegaly was made by	
Endocrinologist	40 (69%)
Internal medicine	10 (17.2%)
Neurosurgeon	6 (10.2%)
Family doctor	1 (1.8%)
Gynecologist	1 (1.8%)
Initial complaints at diagnosis (number of patients)	
Headache	10
Hypertension	30
Fatigue/lack of energy	32
Heart disease	12
Thyroid nodules	32
Sleep apnea	14
Diabetes	24
Polyposis coli	14
Back pain	5
Neuropathic symptoms	9
Joint pain	30
Mood disorder	16
Visual disturbance	8
Skin problems	22
Menstrual irregularities	5
Weight gain	2
Galactorrhea	2
Excessive body hair	2
Distortion of the facial structures	7
Teeth abnormality	1

Patients' disease perception, symptoms, and diagnostic process

Of the 58 patients, 30 (51.7%) knew the etiology of their disease (that they had a GH-secreting pituitary adenoma), while 28 (48.3%) could not define it. None of the patients knew another acromegaly patient among their family members or close friends.

Median year until diagnosis after symptom onset was 2 years (min-max; 1–12 years). Symptoms were identified by the patient him/herself in 12 (20.7%) cases, by a family member in 4 (6.9%) cases, and with the help of the clinical history taken by a health care professional in 42 (72.4%) cases. The diagnosis of acromegaly was made by an endocrinologist in 40 (69%) patients, by an internal medicine doctor in 10 (17.2%) patients, by a neurosurgeon in 6 (10.2%) patients, and by a family doctor and a gynecologist in 2 patients. Among the initial symptoms, headache was present in 10 patients, hypertension in 30 patients, fatigue or lack of energy was present in 32 patients, heart disease (cardiomyopathy/valvular heart disease) in 12 patients, thyroid nodules in 32 patients, sleep apnea in 14 patients, diabetes in 24 patients, polyposis coli in 14 patients, back pain in 5 patients, joint pain in 30 patients, mood disorder in 16 patients, neuropathic symptoms in 9 patients, visual abnormality in 8 patients, skin problems in 22 patients, menstrual irregularities in 5 patients, weight gain in 2 patients, galactorrhea in 2 patients, excessive body hair growth in 2 patients, distortion of facial structures in 7 patients, and teeth abnormality in 1 patient.

Only 9 of 58 patients reported decreased QoL because of the acromegaly-related symptoms. And the most common disturbing symptoms were headache and arthralgia. Three patients reported negative impact of disease in their social life and personal relationships. The most common reason for this was facial disfigurement. Two patients blamed the disease as a reason for their divorce. Twenty patients were not actively working, but none of them thought acromegaly was an obstacle to the occupation status. There were 24 patients who were retired, of whom 12 were admitted for early retirement option due to acromegaly and were receiving disease-related disability privileges. A total of 38 patients reported that they perceive acromegaly as a lifelong disease without a definite cure.

Treatments and disease control status

Of the 58 patients, 56 (96.6%) underwent surgery as the primary treatment. The histopathology revealed a GH-positive pituitary adenoma in 51 patients. Seven patients had combined staining with prolactin (PRL) and GH. The histopathology reports were lacking the granulation pattern. Notably, 46 (79.3%) patients received medical treatment with somatostatin receptor ligands (SSRLs) (e.g., octreotide or lanreotide LAR) with or without cabergoline. Only three patients had complaints due to SSRLs, mostly gastrointestinal discomfort and pain at the injection side. None of the patients received pasireotide or pegvisomant. Of note, 11 (19.6%) patients received radiotherapy (conventional/gamma knife). Mean disease duration was 11.7±4.97 years. After the diagnosis, all patients reported visits to endocrinologists. In all, 20 reported regular visits in every 6 months and the rest 34 patients reported at least one visit in a year. The other specialties that they regularly consulted were a neurosurgeon (19 patients), ophthalmologist (6 patients), and gastroenterologist (12 patients). The number of patients whose IGF-1 was in the target range in the last

two visits was 38 (65.5%). Of the 58 patients, 52 (89.6%) chose the surgery as the most effective treatment, followed by radiotherapy (6.9%) and medical treatment (3.5%). IGF-1 was used in the follow-up of all patients, whereas glucose GH test was used within the previous year only in 6 patients. IGF levels was measured in each visit every 8.9±3.6 months. The frequency of magnetic resonance imaging (MRI) was every 15.6±6.5 months. The diagnosis of acromegaly caused early retirement in 12 patients and the loss of occupation in 2 patients, whereas no major changes were reported in others. Details of the diagnostic process are shown in Table 1, and treatment and follow-up details are shown in Table 2.

Impact of sex difference

Both male and female patients were compared regarding the time interval between the start of the symptoms and diagnosis, treatment modalities received, and disease control status. The median time from the onset of symptoms to diagnosis was 2.3 years (1.5–12) in females and 1.8 years (1–10) in males (p=0.59). Disease duration was 14.3±4.16 years in females and 10.0±4.8 years in males (p=0.03). Demographic and diagnostic features were similar, except the number of patients was higher among men than women (p<0.001). The choice of treatment modalities, the number of patients operated, and medical treatment percentage were similar between two genders (p=0.55, 0.58, and 0.46, respectively). The number of patients in remission was also similar between two genders (p=0.17) (Table 3).

Table 2. Treatment and follow-up details.

Number of patients operated as primary treatment	56 (99.6%)
Number of patients operated more than once	24 (41.3%)
Number of patients treated with SSRLs	46 (79.3%)
Number of patients received radiotherapy (conventional/gamma knife)	11(19.6%)
Mean disease duration (years)	11.7±4.97
Mean interval between control visits (months)	8.9±3.6
Number of patients going regular control visits to	
Endocrinologist	58 (100%)
Neurosurgeon	19 (32.7%)
Ophthalmologist	6 (10.3%)
Gastroenterologist	12 (20.6%)
Number of patients in remission (IGF-1 in normal range)	38 (65.5%)
Test used in the follow-up	
IGF-1	58 (100%)
Glucose growth hormone suppression test	6 (10.3%)
MR (periodically)	22 (37.9%)

DISCUSSION

In this study, we evaluated the demographic and social features, diagnostic process, access to treatment, follow-up procedures, and perception of disease by the patient in our single-center acromegaly patients. Our hospital is a tertiary center with an experienced endocrinology clinic with registered acromegaly patients. We enrolled 58 of those who gave consent and accepted to fill the detailed study forms and answer the questions.

In this patient cohort, the diagnostic process started with the recognition of the first disease-specific symptom until the exact diagnosis was 2 years (min-max: 1–12). In a previous study, it was reported that the delay was longer, with an average of 5.3±4 years from symptom onset[2]; however in recent studies, it has become shorter, with an average of 2.5 years[4,5]. In a previous cohort with higher number of patients from Turkey, the median period of delay before the initial diagnosis was 24 months and interquartile range was 6.0–48.0 months[8]. The possible explanations for relatively shorter diagnostic process may be due to living in the capital city and easy access of patients to the endocrinologists or internal medicine doctors without loosing time for referral from the family practitioner. Also, it may be due to the "acromegaly awareness" courses and educational workshops for physicians by the Endocrinology and Metabolism society in our country. We did not show any difference between genders, indicating that both genders equally benefit from the health care facilities. This may also be due to similar education levels of two genders.

The education level was similar between the genders, and unfortunately low with >50% of the patients did not graduate from high school. We do not know the educational level of the background population composed of age- and sex-matched

Table 3. Comparison of male and female patients according to diagnosis time and access to treatment.

	Female (24)	Male (34)	
Time to diagnose (years) (median)	2.3 (1.5–12)	1.8 (1–10)	p=0.59
Disease duration (years) (mean)	14.3±4.16	10.0±4.8	p=0.03
The number of patients operated	24 (100%)	32 (94.1%)	p=0.58
Usage of SSRLs or DA	19 (79.1%)	27 (79.4%)	p=0.46
Number of patients in remission	16 (66.6%)	22 (64.7%)	p=0.17

healthy individuals to make a comment. In a recent study, it was reported that the education status of the acromegaly patients was similar to the general population, except a tendency toward lower educational level especially in patients diagnosed before 30 years of age[9].

In the context of daily life, there were no significant changes in personal or social life. The marital status changed only in two female patients because of the acromegaly diagnosis. Half of the patients who were retired had early retirement. Our data support that acromegaly reduces work life and production. In a previous study, it was shown that the comorbid conditions such as diabetes, cardiac disorders, or debilitating arthropathy increase the early retirement, and this rate increases with time and is more prominent in females[10-12]. The number of active workers were higher in males, reflecting the occupation ratios of our reference population. Participants recognized that they had a disease for which the word "cure" does not often apply, particularly if they had to face being on medication for the rest of their life. In our patient group, all the participants reported in one way or another by the degree to which they had educated themselves about the disease via online sources and their own experiences, then additionally through listening to and sharing with each other.

Concerns raised by a doctor or another health care professional prompted the diagnosis in most cases. Patients and close friends or relatives suspected the disease in a low number of cases. In our cohort, most of the patients came to medical attention with nonspecific findings at the time of diagnosis. More specific features such as facial features or extremities were detected less by the patients. So, in most cases, the diagnosis was incidental and caught by the attention of the doctor, as reported in previous studies[4,13,14]. Most of the patients were diagnosed with acromegaly by an endocrinologist or an internal medicine doctor. The diagnosis was made by the suspicion of the physician during examination of related comorbidity or complications, including thyroid nodular disease, diabetes, and hypertension in most cases. The cases detected by the neurosurgeons were mostly admitted with compressive symptoms due to adenoma such as headache or visual abnormality. The number of patients detected by general physicians (GPs) was less and none were referred from the dentist in contrast to previous studies[15,16].

Diagnostic and treatment modalities are in line with international guidelines in our country[17]. The most preferred primary treatment in patients was surgery, which was also perceived as the most effective treatment by the patients. Surgery could not be performed in two patients because of preoperative risk due to advanced cardiopulmonary disease. Almost 40% of the operated subjects underwent recurrent surgeries. Our findings were compatible with the previous reports, suggesting that the remission rates are lower than 60% for macroadenomas[18]. SSRLs and DA were used for medical therapy in patients who could not achieve remission after the surgery. Access to medical treatment and remission rates were similar between male and female patients. The remission rate with medical treatment was over 60%, which was higher than a recent report[19].

CONCLUSION

The symptom in acromegaly patients is usually detected by clinicians incidentally, so diagnosis requires attention, knowledge, and suspicion. Patients do not have severe alterations in daily or social life, but occupation is decreased due to comorbid conditions. To decrease economic burden of the disease, early diagnosis should be supported by increasing disease awareness among health care professionals and society.

AUTHORS' CONTRIBUTIONS

AD: Conceptualization, Methodology, Writing – original draft. **BP:** Methodology, Writing – original draft. **BG:** Data curation, Investigation. **ÇK:** Data curation, Investigation. **BÇ:** Methodology, Writing – review & editing.

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