

# QUALITY OF LIFE OF PATIENTS WITH SOMATOTROPINOMAS WHO HAVE UNDERGONE VARIOUS TYPES OF TREATMENT

Dyussebekov Yermek Kavtaevich, Dossanova Ainur Kassimbekovna, Bazarbekova Rimma Bazarbekovna, Kazaryan Svetlana Usikovna

JSC «Kazakh Medical University of Continuing Education»

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## ABSTRACT

Acromegaly is a severe neuroendocrine disease which, if not adequately treated, leads to early disability and premature death. Despite the improvement of treatment methods, mortality in this cohort of patients is 2-4 times higher than in the population [1]. Women are mainly affected by this disease [2]. Achieving the goals of biochemical control of acromegaly is considered to be a positive effect of treatment [5,22], but in reality, the situation is significantly aggravated by the presence of various complications and concomitant diseases in patients, which significantly reduce their quality of life [3,4,21].

**Key words:** quality of life, somatotropinoma, acromegaly, AcroQoL questionnaire, ASBQ questionnaire.

### Correspondence:

Dyussebekov Yermek Kavtaevich,  
Dossanova Ainur Kassimbekovna,  
Bazarbekova Rimma Bazarbekovna,  
Kazaryan Svetlana Usikovna  
JSC «Kazakh Medical University of Continuing Education»  
Email: ak.dossanova@gmail.com  
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## INTRODUCTION

Acromegaly is a disease with multiple organ damage, which is characterized by external changes, an increase in parenchymal organs, multiple comorbidity (including cardiovascular disease and impaired carbohydrate metabolism) and a reduction in life expectancy [1-3]. In addition, with acromegaly, psychological disorders, such as mood swings, low self-esteem, and difficulties in relationships with other people, are common [3,16], as shown by studies conducted using both general and disease-specific questionnaires for patients with acromegaly [4-8].

The goals of treatment for acromegaly include achieving biochemical control, regression of clinical symptoms, control over the volume of growth hormones while maintaining pituitary functions, treatment of concomitant diseases, improving the quality and life expectancy [11, 12, 17]. The concept of “biochemical control” in acromegaly is determined by strict hormonal criteria that must be achieved and maintained throughout the patient’s life: the level of growth hormone (GH) in a single determination should be less than 2 ng / ml when using standard sets or less than 1 ng / ml when use of supersensitive sets; the minimum level of GR during the test with glucose load should be less than 1 ng / ml when using standard kits or less than 0.4 ng / ml when using supersensitive kits; the level of IRF-1 should correspond to reference values corresponding to the gender and age of the patient [1, 12, 16, 18]. These biochemical criteria were developed during long-term epidemiological studies, which showed that when maintaining precisely such levels of GR and IRF-1 in patients with acromegaly, life expectancy becomes comparable with population indicators, including mortality from cardiovascular and oncological diseases, the leading cause’s mortality with acromegaly [8, 9].

Possible treatments for acromegaly include neurosurgical removal of somatotropinomas, drug treatment, and radiation methods for treating the tumor. Neurosurgical treatment (transsphenoid adenectomy) is recommended as the first line of treatment in most patients with acromegaly who do not have somatic contraindications for surgical intervention [21-25]. However, the outcome of neurosurgical treatment depends on

many factors, among which the size of somatotropinomas and the qualifications of a neurosurgeon are important [9, 10, 25]. The ultimate goal of surgical treatment is not just the lack of imaging of the tumor, but the achievement of the biochemical criteria for disease control described above. Therefore, after the operation, a hormonal examination must be performed, usually not earlier than 12 weeks after the operation, including determining the level of IRF-1 and a single determination of GR, as well as a test with a glucose load [1, 2, 17]. Biochemical control is usually achieved. 70–75% of patients with growth hormones localized within the sella, and only 10–33% of patients with pituitary tumors extending beyond it. Based on this the purpose of the study was to study the quality of life of patients with somatotropinomas who received different types of therapy at different times.

## MATERIAL AND METHODS

We examined 60 patients aged 20 to 62 years who were treated for acromegaly. All of them underwent a transnasaltransfenoidaladenectomy using a neuronavigator. In addition to surgical treatment, all 60 patients received medication and it consisted in the use of an analogue of somatostatin, somatullin. Moreover, 31 patients (group 1) from additional methods received only drug therapy, 29 people (2 groups) also received radiation therapy. We evaluated quality of life using ASBQ and AcroQuality of life questionnaires. Correlation analysis did not reveal a reliable relationship between quality of life and sex ( $r = 0.1$ ), and there was no dependence of quality of life on age ( $r = 0.09$ ).

The analysis of the ASBQ data showed that very low quality of life, which occurred in all patients with somatotropinomas before the operation, increased significantly 1-3 months after the operation. We obtained slightly different results in the evaluation of quality of life several years after the operation, which was directly related to the treatment methods used. Thus, the patients of the 1st group had relatively good quality of life, in general, comparable to the indicators in the first 1-3 months after the operation. Patients of the 2nd group, who received triple therapy, had lower values of quality of life in terms of physical activity, endurance and pain. Emotional

sphere was the least affected in all time intervals in all patients surveyed, contrary to expectations.

The Wilcoxon calculation confirmed the data obtained. Thus, in the postoperative period after 1-3 months there was a significant increase in the number of quality of life in patients with somatotropinomas in all parameters. Further, a few years after the operation the quality of life of patients of the 1st group continued to improve significantly. Patients of the 2nd group, who received additional radiotherapy, did not have any reliable difference in physical activity, endurance and pain in comparison with the data after 1-3 months of operation.

Acromegaly is a severe neuroendocrine disease which, if not adequately treated, leads to early disability and premature death. Despite the improvement of treatment methods, mortality in this cohort of patients is 2-4 times higher than in the population [1]. Women are mainly affected by this disease [2].

Acromegaly is a slowly progressing disease, so its diagnosis at the beginning of the disease is difficult. According to Dreval A.V. et al., it is diagnosed on average 6-8 years after its onset [5].

The positive effect of treatment is considered to be the achievement of the goals of biochemical control of acromegaly [5], but in reality the situation is significantly aggravated by the presence in patients of various complications and concomitant diseases that significantly reduce their quality of life (quality of life). Factors that reduce QI in patients with this disease include changes in appearance, depression, headaches, arthralgia, reduced libido, sexual dysfunction, etc. [3,4]. Surgical, radial, drug, and combined methods are used in the treatment of acromegaly. Each of them can both improve and worsen the fertility of patients [1]. Thus, for example, surgical and radial methods of treatment lead to the development of hypopituitarism [1], medical - to disorders of carbohydrate metabolism, the formation of gallbladder stones, etc. [13-15].

If in the 30-50s of the last century the main criterion of efficacy of neurosurgical treatment of patients, including those with pituitary gland adenomas, was the lethality index, which at that time exceeded 50% [6,7], nowadays, due to the decrease in postoperative lethality, the treatment results are usually evaluated by the degree of radicality of the operation, the probability of recurrence of tumors and quality of life patients [8].

Special questionnaires serve as the basic tools for assessment of quality of life [6,9].

**Table 1. Sex-age group of operated patients**

Age	Women 44/73,3%		Men 44/73,3%		Both sex	
	Abc	%	Abc	%	Abc	%
Up to 20	0	0	1	6,3	1	1,6
20-29	7	15,9	2	12,5	9	15
30-39	10	22,7	4	25,0	14	23,3
40-49	8	18,2	5	31,3	13	21,7
50-59	15	34,1	4	25,0	19	31,7
Above 60	4	9,1	0	0	4	6,7
<b>Total</b>	<b>44</b>	<b>100</b>	<b>16</b>	<b>100</b>	<b>60</b>	<b>100%</b>

As can be seen from Table 1, women dominated our study almost three times (2.74 times). Among women, the highest number of cases (34.1%) was in the age group 50 to 59 years old, and among men in the age group 40 to 49 years old

(31.3%). The size of the pituitary gland adenoma was estimated according to the Kadashev B.A. classification [13] (Table 2).

**Table 2. Distribution of patients by size of pituitary adenoma**

Type of pituitary adenoma	Microadenomas (up to 15 mm)	Small ones. (16 – 25 mm)	Medium (26 – 35 mm)	Big (36 – 59 mm)	Gigant (60 mm & more)
<b>Somatotropinoma</b>	16/ %	17	27	-	-

All patients were treated in 2007-2017. All of them underwent transnasaltransfenoidaladenectomy with the use of BRAINLAB neuronavigator.

Surgical intervention in 48 (80%) patients was carried out in the conditions of the city clinical hospital №7 in Almaty, Kazakhstan, 12 (20%) patients were operated on in other medical institutions.

According to our clinic, total adenectomy is performed in 75% of cases. This study included only patients who for one reason or another failed to perform a total adenectomy. Radiation and drug therapies were used as additional treatment methods (Table 3).

**Table 3. Types of treatment used for the treatment of somatotropinoma patients**

Treatment types	Surgical removal + medication	Surgical removal + radiotherapy + drug therapy
Type of adenoma	Group 1	Group 2
<b>Somatotropinoma</b>	31	29

In addition to the surgical treatment, all 60 patients received medication and it consisted of the use of an analogue of somatostatin, somatullin. Moreover, 31 patients (group 1) of the additional methods received only drug therapy, 29 people (group 2) also received radiation therapy (Table 3).

Radiation therapy was performed using the True Beam Radiotherapy System linear accelerator (Varian Medical Systems, Inc.) with standard fractionation (25-30 sessions, 45-50 gray).

We evaluated quality of life using ASBQ and AcroQoL questionnaires. The ASBQ questionnaire [13] is designed to evaluate the QI of patients treated for various skull base masses, including AH.

This questionnaire contains questions that give an idea of the different aspects of a patient's life. The questions are grouped into blocks: 6 questions for overall productivity, 7 questions for physical activity, 7 questions for endurance (energy), 7 questions for pain, 3 questions for pain, 5 questions for emotions, and 7 questions for specific symptoms (sense of smell, taste, vision, etc.).

The answers are evaluated on a five-point scale, with a negative answer corresponding to 1 point and a positive answer to 5 points. The structure of the questionnaire allows for a detailed assessment of the impact of various factors on Quality of life in general and its various components.

**Table 4. Quality of life of patients with somatotropinomas according to the ASBQ questionnaire before surgery and several years after surgery**

The AcroQoL questionnaire is designed specifically for the assessment of CS in patients with somatotropinoma [11-12].

Quality of life evaluation period	Group 1			Group 2		
	p <sub>1</sub>	p <sub>2</sub>	p <sub>3</sub>	p <sub>1</sub>	p <sub>2</sub>	p <sub>3</sub>
Units						
Productivity	0,001	0,002	0,0001	0,0001	0,021	0,0001
Physical activity	0,0001	0,011	0,0001	0,0001	0,015	0,1
Endurance	0,0001	0,002	0,0001	0,0001	0,092	0,11
Pain...	0,0001	0,004	0,0001	0,007	0,007	0,6
Emotions	0,0001	0,005	0,0001	0,001	0,007	0,001
Specific symptoms	0,0001	0,002	0,0001	0,001	0,002	0,0001

Patient responses are evaluated on a five-point Likert scale. The higher the sum of points, the higher the quality of life.

This questionnaire contains 22 questions, which are divided into two scales (groups) defining psychological (14 questions) and physical (8 questions) aspects of life. In turn, the psychological scale consists of two parts, each of which has 7 points: the first part evaluates the impact on the Quality of life appearance, the second part evaluates the impact of the disease on the patient's private life.

The questions concerning the frequency of the symptom occurrence have possible answers in the range "Always" - "Never". For questions regarding the degree of patient's agreement with some statement, answers are offered from "Fully Agree" to "Fully Disagree".

To standardize the results of the survey, the developers suggest using the following formula:

$$\text{Quality of life (points)} = [(X - \text{min}) / (\text{max} - \text{min})] \times 100,$$

Statistical processing of the results was carried out by the Wilcoxon method. The correlation analysis was also carried out. For the sake of clarity, graphs were drawn up - aradars, in which the minimum score corresponded to 1, and the maximum -5 with the use of Microsoft Excel software package.

Quality of life evaluation period	Group 1			Group 2		
	p <sub>1</sub>	p <sub>2</sub>	p <sub>3</sub>	p <sub>1</sub>	p <sub>2</sub>	p <sub>3</sub>
Units						
Self-perception	0,0001	0,0001	0,0001	0,502	0,001	0,002
Personal.	0,001	0,0001	0,002	0,005	0,001	0,001
interrelationships	0,0001	0,0001	0,0001	0,001	0,101	0,001

**RESULTS**

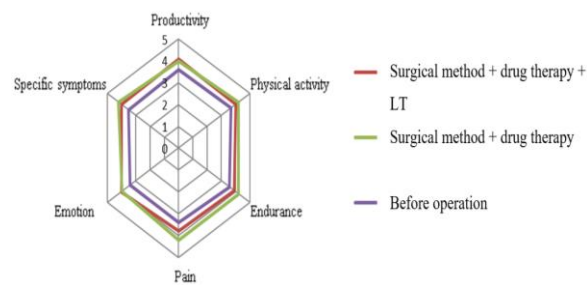
Correlation analysis did not reveal a reliable relationship between Quality of life and sex (r = 0.1), no dependence of quality of life on age (r = 0.09).

Figures 1,2 below presents quality of life in patients with somatotropinomas in the preoperative period, in the first 1-3 months and several years after the operation according to the ASBQ questionnaire. Each axis shows the average value of Quality of life for the blocks described above, while a higher score indicates a higher level of Quality of life : the highest score -5, the lowest -0.

As can be seen from figures 1,2, the very low level of quality of life in all patients with somatotropinomas before the operation (inner violet polygon) increased significantly 1-3 months after the operation (red and green polygons).

We obtained slightly different results in the evaluation of quality of life several years after the operation, which was directly related to the treatment methods used. Thus, the patients of the 1st group had relatively good quality of life, in general, comparable to the indicators in the first 1-3 months after the operation. Patients of the 2nd group, who received triple therapy, had lower values of quality of life in terms of physical activity, endurance and pain. Emotional sphere was the least affected in all time intervals in all patients surveyed, contrary to expectations (Figures 1,2).

**Figure 1. Quality of life of somatotropinoma patients according to the ASBQ questionnaire before and after 1-3 months after surgery**



**Figure 2. Quality of life of somatotropinoma patients according to the ASBQ questionnaire prior to surgery and several years after surgery.**

The data obtained were confirmed by an analysis of the ASBQ survey results using the Wilcoxon method. Table 4 shows that in the postoperative period after 1-3 months there was a significant increase in the quality of life in patients with somatotropinomas in all parameters. Further, several years after the operation the quality of life of patients of the 1st group continued to improve significantly. Patients of the 2nd group, who received additional radiotherapy, did not have any reliable difference in physical activity, endurance and pain in comparison with the data after 1-3 months of operation (Table

**Table 5: Analysis of AcroQL questionnaire data**

p1 - when comparing data before the operation and 1-3 months after it

p2 - when comparing data in 1-3 months and a few years after that

p2 - when comparing data before the operation and several years after it

Analysis of the AcroQoL questionnaire data using the Wilcoxon method showed an improvement in QI in both groups, both months and years after surgery. However, Group 2 patients had no significant changes in self-perception 1-3 months after the operation, which subsequently improved. It is important to note that in the patients of group 2 the physical aspects of quality of life improved significantly in 1-3 months after adenomectomy (Table 5).

p1 - when comparing data before the operation and 1-3 months after it

p2 - when comparing data in 1-3 months and a few years after that

p3 - when comparing data before the operation and several years after it

## CONCLUSION

Despite the fact that quality of life is generally characterized as "benign", it significantly reduce the number of quality of life patients, leading to severe medical and social consequences [13, 18, 19]. The key to good quality of life after surgery is total removal of the tumor (4,8). We have shown that there is no reliable connection between the sex and age of patients with somatotropinoma.

Analysis of the ASBQ questionnaire data showed a significant increase in Quality of life in all patients with somatotropinomas 1-3 months after surgery. However, several years after the operation, the additional treatment method used directly depends on the patient. Thus, patients receiving radiation therapy had worse physical activity, endurance and pain indicators. It is important to note that the emotional sphere of both groups of patients suffered the least in all time periods.

Our data are consistent with the results of the Chudakova I.V.'s study, which also shows that the QI of patients with pituitary gland adenomas, having increased in the months after surgery, then stabilizes and does not change over a long period of time [19-21].

A detailed study of the results of the answers to the questions of the specific AcroQoL questionnaire of the patients we examined revealed a significant improvement of the Quality of life in both groups, both several months and several years after the operation, except for the indicator "physical aspects of life".

Similar results are shown in the study of Dreval A.V. et al. It was revealed that the Quality of life of patients with acromegaly according to the AcroQoL questionnaire as a whole does not depend on the level of insulin-like growth factor of type 1 and does not differ in patients with controlled and uncontrollable course of the disease. Comparison of patients with first detected acromegaly with previously treated patients revealed reliable differences only in the parameters "general quality of life associated with health" and "physical condition" [15].

The Consensus on Acromegaly Treatment, 2018, also states that the use of a specific AcroQuality of life questionnaire is of limited importance, probably due to its lack of objectivity [14,15]. Based on the foregoing, two main conclusions follow:

1. The quality of life of patients with somatotropinomas who have undergone various types of treatment significantly improves after neurosurgical treatment.

2. It is further improved by the use of somatostatin analogues as an additional treatment, and to a lesser extent - radiotherapy.

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