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ORIGINAL ARTICLE

Biliary Tract Disorders in Patients with Acromegaly: Single-centre Experience

Süleyman Nahit Şendur[1]
ORCID: 0000-0001-6740-6708

Seda Hanife Oğuz[1]
ORCID: 0000-0002-7781-944X

[1]Hacettepe University, Faculty of Medicine, Department of Endocrinology & Metabolism, Ankara, Turkey.

Corresponding Author: Süleyman Nahit Şendur
Hacettepe University, Faculty of Medicine, Department of Endocrinology & Metabolism, Ankara, Turkey.
E-mail: snahitsendur@hotmail.com

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ABSTRACT

Objective: Genetic and environmental factors determine the risk of biliary tract disorders. Several studies have reported an increased frequency of gallbladder disorders in patients with acromegaly belonging to different ethnic groups, however, data for Turkish patients with acromegaly is currently lacking. The primary objective of this study was to evaluate the frequency of diverse gallbladder disorders in Turkish patients with acromegaly. The secondary objective was to determine the risk factors that are related to gallstone formation.

Materials and Methods: Hacettepe University electronic database was retrospectively analyzed. One hundred fifty-two out of 393 patients with acromegaly who had confirmed biliary tract disorders with imaging modalities (such as abdominal ultrasonography, abdominal computed tomography or abdominal magnetic resonance imaging) or surgery specimens, were included for final analyzes. There was not any difference between included and excluded cases in terms of study parameters.

Results: Patients with acromegaly with a mean±SD age of 41±12 years were followed-up for median of 91 months. Gender distribution was equal (76 M, 76 F). Gallstones were detected in 50 (33%) cases. Seventeen (11%) cases had gallbladder sludge whereas 5 (3%) cases had gallbladder polyp. Cholecystectomy was performed in 24 (16%). Age, gender, baseline disease activity, diagnostic delay, disease duration, the presence of type 2 diabetes mellitus and hyperlipidemia were not associated with gallstone formation. Body mass index (β=1.19, 95% CI (1.09-1.30), p<0.001) and somatostatin receptor ligand use (β=3.8, 95% CI (1.2-12.6), p=0.026) were determined as independent risk factors for cholelithiasis.

Conclusions: Biliary tract disorders are common in Turkish patients with acromegaly. Acromegaly patients with high body mass index and on somatostatin receptor ligand treatment had an increased risk for gallstone disease.

Keywords: Acromegaly, gallbladder, cholecystolithiasis, cholelithiasis, polyp, sludge, somatostatin receptor ligand

INTRODUCTION

Acromegaly is a unique disorder characterized by chronic growth hormone (GH) and insulin-like growth factor-1 (IGF-1) hypersecretion. Over 95% of the cases a GH-secreting pituitary adenoma arising from somatotroph cells causes GH overproduction; rarely, growth hormone-releasing hormone secretion from a neuroendocrine tumor or more rarely, ectopic GH release by an abdominal or hematopoietic tumor may result in acromegaly [1].

Chronic exposure to excess GH and IGF-1 leads to systemic manifestations and, gastrointestinal and hepatobiliary disorders are frequently encountered in patients with acromegaly [2]. For instance, bowel length increases up to 20% [3]. Colonic diverticulosis is common; hyperplastic and adenomatous polyps could be seen and both are associated with disease activation [4,5]. Colorectal cancer risk has been shown to be higher [6]. There is an increased prevalence of gallbladder polyps in patients with acromegaly and the risk is higher in patients with higher GH levels [7]. Not disease activity per se however, somatostatin receptor ligands (SRLs) which are the mainstay of the medical management of acromegaly, induce gallstone and sludge formation and, several studies have reported increased frequency of gallstone disease with varying proportions in patients with acromegaly belonging to different ethnicities [8-10].

In this study, we aimed to evaluate the frequency of biliary tract disorders and the predictive factors for the biliary tract stone onset in a large population of Turkish patients with acromegaly.

MATERIALS AND METHODS

Study design, study population and study parameters

Data of 393 patients with acromegaly who were followed up between 1980 and 2018 at the Department of Endocrinology and Metabolism, Hacettepe University, Ankara, Turkey were retrospectively analyzed. As shown in the inclusion diagram (Figure 1), final analyzes were performed in 152 patients with biliary disorders that were confirmed with imaging modalities such as hepatobiliary ultrasonography, abdominal computed tomography, abdominal magnetic resonance imaging and/or surgery specimens. There were no differences between included and excluded cases in terms of study parameters.

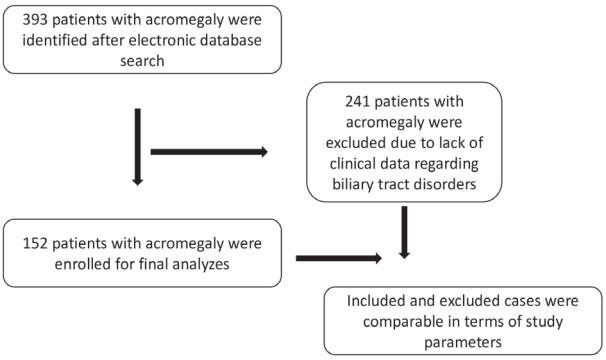

Figure 1. Inclusion diagram

For each patient, the following data were recorded: age at the diagnosis of acromegaly (years), age at the first symptoms related to acromegaly (years), gender, time from symptoms to diagnosis (years), disease duration (years), follow-up duration (months), height (cm), weight (kg), body mass index (BMI) (kg/m2), GH level at diagnosis (ng/mL), IGF-1 level at diagnosis (ng/mL), adenoma size (mm), first-line treatment for acromegaly, medications for acromegaly, presence of type 2 diabetes mellitus and hyperlipidemia. Based on the imaging and surgery data, information relative to gallstones, sludge, gallbladder polyps and cholecystectomy was collected.

The study was conducted in accordance with guidelines in the Declaration of Helsinki and its later amendments. Hacettepe University Ethical Board approved the study with the project number GO 19/303.

Statistical analysis

All analyzes were performed with Statistical Package for Social Sciences (SPSS) version 21.0. The distributions of continuous variables were tested for normality by using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test). Descriptive measures of variables with normal distribution were presented as the mean ± standard deviation. Median-interquartile range (IQR) was used to describe continuous variables with a skewed distribution. Categorical variables

were expressed as frequencies and/or percentages where appropriate. Student's t-test and Mann-Whitney U test were used to compare differences in normally distributed and non-normally distributed continuous variables, respectively. The differences in categorical variables were assessed by The Chi-square or Fisher's exact test. While investigating the associations between variables, the correlation coefficients and their significance were calculated using the Pearson or the Spearman tests. For the multivariate analysis, the possible factors identified with univariate analysis were further entered into the regression analysis to determine independent predictors of the presence of cholecystolithiasis. The model fit was assessed using appropriate residual and goodness-of-fit statistics. A 5% type-1 error level was used to infer statistical significance. A p-value ≤ 0.05 was accepted as statistically significant.

RESULTS

Demographic, clinical and biochemical characteristics of patients with acromegaly

Demographic, clinical and biochemical characteristics of patients with acromegaly were summarized in Table 1.

Accordingly, the mean age at the diagnosis of patients with acromegaly was 41±12 years. Diagnostic delay was median (IQR) of 2 (0-5) years from the onset of the first symptoms. Patients with acromegaly had a disease duration of 17±10 years and the median (IQR) follow-up length was 91 (37-164) months. Gender distribution was equal (76 male and 76 female) and the patients with acromegaly were mostly overweight or slightly obese; mean±SD BMI 31.9±7.6 kg/m2. GH and IGF-1 levels at diagnosis were 10.4 (5.0-30.4) ng/mL and 859 (608-1079) ng/mL, respectively. All patients had pituitary adenomas as the culprit lesions of excess GH secretion. The size of pituitary adenoma was available in 132 patients and in the vast majority of patients, adenoma was larger than 10 mm; mean±SD adenoma size 18.1±9.2 mm, 82% macroadenoma. Almost in all patients (97%), transsphenoidal surgery was performed as first-line treatment. Three patients were not suitable candidates for surgery due to high surgery risk. Remission could not be achieved with surgery

Table 1. Demographic, clinical and biochemical characteristics of patients with acromegaly, n=152

Parameter	Value
Age at the diagnosis of acromegaly (years)	41±12
Age at the first symptoms related to acromegaly (years)	37±12
Time from symptoms to diagnose (years) *	2 (0-5)
Disease duration (years)	17±10
Follow-up duration (months) *	91 (37-164)
Gender F-M n (%)	76-76 (50-50)
Height (cm)	166±12
Weight (cm)	86±17
Body mass index (kg/m^2)	31.9±7.6
GH level at diagnosis (ng/mL)*	10.4 (5.0-30.4)
IGF-1 level at diagnosis (ng/mL)*	859 (608-1079)
Adenoma size (mm)**	18.1±9.2
Macroadenoma n (%)	100 (82)
Microadenoma n (%)	22 (18)
First-line treatment n (%)	
Surgery	146 (97)
Radiotherapy	0 (0)
Medical treatment	4 (3)
Medical treatment n (%)	
SRL	
Yes	100 (67)
No	49 (33)
Pegvisomant	
Yes	7 (5)
No	141 (95)
Cabergoline	
Yes	28 (19)
No	119 (81)
Type 2 diabetes mellitus n (%)	
Yes	56 (38)
No	91 (62)
Hyperlipidemia n (%)	
Yes	51 (36)
No	92 (64)
Gallbladder disorders n (%)	
Cholecystolithiasis	
Yes	50 (33)
No	102 (67)
Galbladder sludge	
Yes	17 (11)
No	135 (89)
Polyp	
Yes	5 (3)
No	147 (97)
Surgery for gallbladder	
Yes	24 (16)
No	128 (84)

*The data was given as median (interquartile range)

**Adenoma size data was not avaliable in 30 patients

in most of the patients and medical treatment was initiated. While most patients were under SRLs (67%), 5% and 19% of cases were using pegvisomant and cabergoline, respectively. Nearly one in third of patients with acromegaly had type 2 diabetes mellitus (38%) or hyperlipidemia (36%).

Gallstones were detected in 50 (33%) cases and 17 (11%) cases had gallbladder sludge whereas 5 (3%) cases had gallbladder polyps. Cholecystectomy was performed in 24 (16%) patients with acromegaly without any complications.

Determination of risk factors for gallstone disorder in univariate and multivariate analyses

There were not any differences between patients with gallstones and patients without gallstones in terms of age at the diagnosis of acromegaly, age at the first symptoms related to acromegaly, diagnostic delay, disease duration, gender, GH and IGF-1 levels at diagnosis, first-line treatment modalities, the frequency of type 2 diabetes mellitus and the frequency of hyperlipidemia (Table 2).

Patients with cholecystolithiasis were heavier and had a higher BMI; weight (kg), patients with

Table 2. Comparison of risk factors between patients without and with cholecystolithiasis, n=152

Parameter	Patients without gallstone n= 102	Patients with gallstone n= 50	p value
Age at the diagnosis of acromegaly (years)	41.4±11.7	40.1±12.0	0.53
Age at the first symptoms related to acromegaly (years)	37.2±11.6	37.3±12.3	0.95
Time from symptoms to diagnose (years)	3 (0-5)	2 (0-5)	0.41
Disease duration (years)	18.3±9.8	16.9±9.6	0.42
Gender F-M n (%)	48-53 (48-52)	28-23 (55-45)	0.39
Height (cm)	168±12	160±11	**<0.001**
Weight (cm)	82±15	94±17	**<0.001**
Body mass index (kg/m^2)	28.8±5.4	37.3±8.0	**<0.001**
GH level at diagnosis (ng/mL)*	10.1 (5.1-29.5)	10.8 (4.0-34.7)	0.97
IGF-1 level at diagnosis (ng/mL)*	833 (554-1070)	878 (722-1088)	0.38
Adenom size (mm)**	17.0±8.5	20.6±10.3	
Macroadenom n (%)	64 (77)	36 (92)	**0.042**
Microadenom n (%)	19 (23)	3 (8)	
First-line treatment n (%)			
Surgery	97 (97)	49 (98)	0.72
Radiotherapy	0	0	
Medical treatment	3 (3)	1 (2)	
Medical treatment n (%)			
SRL			
Yes	57 (58)	43 (86)	<0.001
No	42 (42)	7 (14)	
Pegvisomant			
Yes	2 (2)	5 (10)	0.031
No	96 (98)	45 (90)	
Cabergoline			
Yes	18 (19)	10 (20)	0.83
No	79 (81)	40 (80)	
Type 2 diabetes mellitus n (%)			
Yes	34 (35)	22 (44)	0.37
No	63 (65)	28 (56)	
Hyperlipidemia n (%)			
Yes	63 (66)	29 (60)	0.58
No	32 (34)	19 (40)	

*The data was given as median (interquartile range)

**Adenoma size data was not avaliable in 30 patients

gallstone 94±17 vs patients without gallstone 82±15, p<0.001; BMI (kg/m2), patients with gallstone 37.3±8.0 vs patients without gallstone 28.8±5.4, p<0.001. Adenomas were larger in patients with gallstone; macroadenoma frequency 92% vs 77%, p= 0.042. Patients were more frequently on SRL or pegvisomant therapy in gallstone group; SRL 86% vs 58%, p<0.001; pegvisomant 10% vs 2%, p=0.031 (Table 2).

Variables determined from univariate analysis were entered into multiple linear regression model to reveal factors that are associated with gallstone formation. As shown in Table 3, among the independent variables, BMI (β=1.19, 95% CI (1.09-1.30), p<0.001) and SRL use (β=3.8, 95% CI (1.2-12.6), p=0.026) were found to be associated with variations in cholecystolithiasis frequency after adjusting for the other co-variables in the model.

Table 3. Risk factors for cholecystolithiasis

Parameter	OR (95%CI)	p value
Somatostatin receptor ligand use	3.8 (1.2-12.6)	0.026
Presence of macroadenoma	1.7 (0.4-7.7)	0.48
Pegvisomant use	4.4 (0.7-28.7)	0.12
Body mass index	1.19 (1.09-1.30)	<0.001

DISCUSSION

The present study has highlighted that biliary tract disorders are frequent in patients with acromegaly. In our cohort, one-third of patients with acromegaly had gallstones and radiologic examinations revealed at least one gallbladder disorder in almost half of the cases. Increased BMI and SRL use were determined as independent risk factors for gallstone formation.

Gallstone disease is common in adult population. The interplay between exogenous factors such as dietary habits and genetic background determines the risk for gallstone formation, therefore the prevalence of gallstone disease varies by geographic region and ethnicity [11]. In Europe, about 20% of the adult population develops gallstones and in the United States, approximately 6% of men and 9% of women have gallstones [12,13]. The risk is highest in Native Americans followed by Hispanic Americans and non-Hispanic Whites. African populations represent the lowest risk group for gallstone disease and the prevalence rates are intermediate in Asian populations varying between 5 to 20% [11,14]. Although there isn't any population-based study assessing the frequency of gallstone disease in the Turkish adult population, Karayalcin et al have found a 15.4% prevalence in a sample of postmenopausal women including 474 females [15]. In our cohort, which included younger individuals and had an equal gender distribution, 33% of patients with acromegaly had gallstone disease. Considering the increased prevalence of gallstone disease in older age and women, it can crudely be said that in our cohort, patients with acromegaly had an increased frequency of gallstone disease when compared to reference Turkish population [11,15].

In addition, gallstones have been variably reported ranging from 3.6 to 56% in patients with acromegaly and in most studies, consistently, the prevalence of gallstone disease has been found to be higher in patients with acromegaly when compared to reference population [9]. However, to date, there is no data regarding the gallstone disease prevalence in Turkish patients with acromegaly. Our study is the first study that evaluates the frequency of gallstone disease in a large cohort of Turkish patients with acromegaly.

Bile is a dark green to yellowish-brown fluid produced by the liver and facilitates the digestion of lipids in intestine. It comprises mainly water (>90%) with bile salts, phospholipids, cholesterol, conjugated bilirubin and electrolytes [16,17]. The generation of cholesterol gallstones is the result of the disruption of cholesterol solubility in bile [18]. Hepatic over-secretion of cholesterol and/or reduced secretion of bile acids and phospholipids lead to an equilibrium that is supersaturated in which bile contains excess amounts of cholesterol that cannot be solubilized by bile salts and phospholipids. Impaired gallbladder emptying, by increasing the residence time of cholesterol-supersaturated bile in the gallbladder lumen, promotes nucleation of cholesterol crystals (sludge) which are the precursors of gallstones. In some cases, prolongation of intestinal transit time contributes to gallstone formation by reducing absorption of bile salts [11].

Hyperinsulinemia induces uptake of cholesterol by hepatocytes and increases biliary secretion of cholesterol [19,20]. Moreover, in the case of

hyperinsulinemia, the excretion of bile acids into the bile is reduced [21]. Consequently, bile is supersaturated and hyperinsulinemic subjects are susceptible to gallstone formation. Due to insulin resistance, patients with obesity have increased insulin levels and obesity is a well-defined risk factor for gallstone disease [22]. Accordingly, patients with obesity are predisposed to gallstone formation, symptomatic gallstones and cholecystectomy [23,24]. In our study, we have found that acromegalic patients with gallstone disease were heavier than their counterparts and for each unit increase in BMI, the risk of cholelithiasis increased ~1.2 times. Thus, obesity is a risk factor for gallstone disease in patients with acromegaly as well.

Transsphenoidal adenoma excision is the first-line treatment in acromegaly but medical treatment is employed in most patients due to inoperable tumors or disease persistence following surgery. SRLs are considered the mainstay in the medical management of acromegaly [1]. These drugs have been used extensively over three decades and overall possess a favorable benefit-risk profile [25]. They are generally well tolerated; the most reported side effects include nausea, diarrhea, abdominal pain and distension. These side effects are self-limited and mainly occur in the first weeks of treatment [26]. It is not surprising that most side effects of these drugs are related to the gastrointestinal system because the hepatobiliary and alimentary tracts are well-defined targets of somatostatin activity [27]. Indeed, SRLs have several actions that may contribute to gallstone formation. They decrease cholecystokinin secretion from small intestine, which is the main stimulator of gallbladder contraction, and inhibit the contractile response of the gallbladder to cholecystokinin [28,29]. By triggering the absorption of sodium and water by the gallbladder, SRLs lead to increase in bile concentration [30]. Moreover, SRLs hinder the physiologic post-prandial relaxation of the Oddi sphincter and promote crystallization and stone formation [31]. Accordingly, several studies have reported an increased prevalence rate of gallstones in patients receiving SRLs either due to acromegaly or other neuroendocrine neoplasms [10,32,33]. Our data confirm that gallstone disease is common in Turkish patients with acromegaly as well and SRL use was the main risk factor for cholelithiasis.

We did not find any associations between the presence of gallstone disease and diagnostic delay, GH level at diagnosis and IGF-1 level at diagnosis. Rather than the activity of acromegaly per se, the most important risk factor for the occurrence of gallstone disease in acromegaly is SRL use which is consistent with previous reports [10,32].

There were particular limitations of our study. Due to the retrospective and cross-sectional design of our study, we could not assess the course of gallbladder disorders and we were not able to collect information regarding the medical treatment of gallstone disease. In addition, there was no information about the status of the gallbladder of the patients before SRL treatment.

In conclusion, gallbladder disorders are frequent in patients with acromegaly. Increased BMI and SRL treatment are the main risk factors for gallstone disease. Clinicians should evaluate the patients with acromegaly, especially the patients who have high BMI and are on SRL treatment, with imaging modalities for early recognition of gallbladder disorders.

Author contribution

Study conception and design: SNŞ and SHO; data collection: SNŞ; analysis and interpretation of results: SNŞ and SHO; draft manuscript preparation: SNŞ and SHO. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Ethical Board (Protocol no. GO-19/303/19.03.2019).

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Conflict of interest

The authors declare that there is no conflict of interest.

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