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Treatments, complications, and healthcare utilization associated with acromegaly: a study in two large United States databases

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Abstract The economic burden of acromegaly in the US has been largely unknown. We describe the prevalence of treatment patterns, complication rates, and associated healthcare utilization and costs of acromegaly in the US. Patients were identified between 1/1/2002 and 12/31/2009 in claims databases. During 1-year after each continuously-enrolled patient's first acromegaly claim, pharmacy and medical claims were used to estimate outcomes. Regression models were used to adjust outcomes. There were 2,171 acromegaly patients (mean age: 45.3 years; 49.7 % female); 77.8 % received the majority of their care from non-endocrinologists. Pharmacologic treatment was used by 30.8 % of patients: octreotide-LAR in 18.6 %, dopamine agonists in 9.8 %, short-acting octreotide in 4.7 %, pegvisomant in 4.1 %, and lanreotide in 1.2 %; 56 % had biochemical monitoring. Comorbidities were common, ranging from 6.6 % (colon neoplasms) to 25.6 % (musculoskeletal abnormalities). Mean healthcare costs were $24,900. Adjusted analyses indicated comorbidities increased the odds of hospitalization: by 76 % for musculoskeletal abnormalities; 193 % for cardiovascular abnormalities; and 56 % for sleep apnea ($p < 0.05$). Odds of emergency department visits increased by 87 % (musculoskeletal) and 132 % (cardiovascular abnormalities) ($p < 0.01$). After adjustments, colon neoplasms were associated with $8,401 mean increase in costs; musculoskeletal abnormalities with $7,502, cardiovascular abnormalities with $13,331, sleep apnea with $10,453, and hypopituitarism with $6,742 ($p < 0.01$). Complications are common and increase utilization and cost in acromegaly patients. Cardiovascular complications nearly tripled the odds of hospitalization (OR 2.93) and increased annual mean cost by $13,331. Adequate management of this disease may be able to reduce health care utilization and cost associated with these complications and with acromegaly in general.

Keywords Acromegaly · Complications · Economics · Treatment · Growth hormone (GH) · Insulin-like growth factor-1 (IGF-1)

Introduction

Acromegaly, a condition caused by excessive growth hormone (GH) production, affects up to 130 individuals per million inhabitants, or as many as 39,000 people in the United States [1]. Clinical features of acromegaly may include acral overgrowth, soft-tissue swelling, arthralgia, sleep apnea, type 2 diabetes, hypertension, and osteoarthritis, respiratory and cardiac failure [2]. In more than 95 % of cases, hypersecretion of GH and subsequent overstimulation of insulin-like growth factor (IGF)-1 production result from a benign pituitary adenoma [3]. In most cases, initial treatment is surgery to remove the adenoma, but about half of patients require additional treatment [3].

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People with acromegaly suffer increased mortality [4]. The risk of cancer in acromegaly patients may be increased compared to the general population, but this is controversial [5]. It has been estimated that up to 70 % of acromegaly patients have skeletal disorders, 60 % have cardiac disease, and 50 % have obstructive sleep apnea at the time of acromegaly diagnosis [2]. However, available estimates of the frequency of these conditions arise from small trials, which may not be representative of the larger acromegaly population [1, 2]. The goal of treatment is to reduce GH and/or IGF-1 secretions to normal levels, as well as improve or prevent these medical co-morbidities, reduce tumor burden, and prevent premature mortality [1].

The distribution of treatment, complications, and economic burden associated with acromegaly in the US population has been largely unknown. A recently published framework for assessing the impact of these complications and the value of their control recommended comparing healthcare utilization and cost between acromegaly patients with and without various complications [1]. We aimed to do this by combining two large, independent, insurance claims data sets to derive a large enough sample of patients with this rare condition. We used the resulting combined database to describe treatment patterns, estimate the prevalence of complications, and estimate the utilization and cost associated with these complications.

Methods

Study design and data sources

We conducted a cross-sectional cohort study of prevalent acromegaly patients using data from two major United States commercial claims databases, Thomson Reuters MarketScan and IMS Health PharMetrics. Each database contains claims for over 10 million covered lives per year. The geographic distribution of patients in the databases is determined by the distribution of specific insurance plans that provide claims data. Both are Health Insurance Portability and Accountability Act compliant and contain de-identified adjudicated claims submitted for payment to several large health plans by providers, healthcare facilities, and pharmacies. Claims in these databases include information about each physician visit, medical procedure, hospitalization, drug dispensed in the outpatient setting, date of service/prescription, number of days of medication supplied, and tests performed. These data also include patient, provider, and hospital demographic information, and member enrollment and benefit information. Healthcare costs (claims paid) are recorded in both databases. The data used in this study spanned the period from 1/1/2002 to 12/31/2008 for the PharMetrics database and from 1/1/2002 to 12/31/2009 for the MarketScan database. The study period consisted of the single calendar year following the date on which the patient qualified for inclusion.

Study population

There is no validated algorithm for identifying patients with acromegaly using claims data. To identify the study group we began by identifying all patients with at least one medical claim with an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis of acromegaly (253.0) during the 7 year period from 1/1/2002 to 12/31/2008 (identification period). A single diagnosis code may represent a coding error or a service designed to rule out the diagnosis. To be included in the study, patients therefore had to have either (1) one additional claim with an ICD-9-CM code for acromegaly or (2) a pituitary tumor (ICD-9-CM 237.0) diagnosis during the 1 year review period (the calendar year after the first observed acromegaly diagnosis). Patients were excluded if they were not continuously enrolled in an eligible health plan for this entire one-year period (and therefore would not have complete claims data for this time period).

The two databases used were entirely independent and contained no personally identifiable information. It is theoretically possible for one patient to be insured by two different plans, one in each database. To avoid including the same patient in the study twice, once from each database, we excluded possible duplicates. We considered a patient identified in one database as a possible duplicate if he or she had the same age, gender, US census region, and date of first medical claim as a patient in the second database. If this occurred, only one of the patients was included in the study.

Study measures

All measures were derived from enrollment files, medical claims, and pharmacy claims submitted in the year following the first observed acromegaly diagnosis. Every claim for an individual's period of enrollment is included in the database, and there are presumed to be no missing data, since a claim must exist in order for payment to be processed. Patient demographic characteristics (age, gender, and US census region) were identified in enrollment records. 'Usual physician specialty' is a validated concept that assigns a specialty to each patient, based on data from claims. In this method, the 'usual physician specialty' is the physician specialty with the largest number of patient office visits coded with evaluation and management services (e.g., those visits that require the physician's cognitive input, as opposed to, for example, visits for laboratory tests or injections) [6]. Two measures of overall burden of illness were calculated.

The number of chronic conditions experienced by each patient was calculated using the Healthcare Cost and Utilization Project Chronic Condition Indicator (CCI) [7, 8]. The extensively-validated CCI defines a chronic condition as a one that generally lasts ≥12 months and either (a) places limitations on self-care, independent living, and social interactions, or (b) results in the need for ongoing intervention with medical products, services, and special equipment. The Charlson Comorbidity Index, initially developed as a predictor of in-hospital mortality, has been adapted and widely reported as a measure of overall burden of illness in the general population [9, 10].

Treatments for acromegaly were identified using Current Procedural Terminology (CPT) codes for tests and procedures, National Drug Codes for orally administered medications, and Healthcare Common Procedure Coding System codes for injected medications ("Appendix in ESM"). Tests of interest were IGF-1 and GH, and these were identified using CPT codes. Using expert endocrinologist (LK) input and literature review, we developed an a priori list of complications that may be associated with the disease and which could be identified in claims (e.g., those for which specific ICD-9-CM codes exist). These complications included colon neoplasms (colon polyp, colon cancer), musculoskeletal problems (osteoarthritis, arthropathy, arthralgia, synovitis, carpal tunnel syndrome), cardiovascular diseases (cardiomyopathy, cardiac hypertrophy, heart failure, cardiac dysrhythmia, arrhythmia), sleep apnea, reproductive system abnormalities (galactorrhea, menstrual abnormality, impaired libido, impotence, infertility), and hypopituitarism. Claims for cardiovascular risk factors (diabetes, hypertension, and hypertriglyceridemia) were also identified. Health care utilization, including number of physician office visits, number of emergency department visits, and number of inpatient hospitalizations, was derived from medical claims. Costs were derived from medical and pharmacy claims and were reported as pharmacy, non-pharmacy, and total costs.

Analyses

Descriptive statistics, including mean, median, standard deviation, and percentage, were reported for all study measures, as applicable. Statistics were produced separately for each database then compared across databases. Results were similar, and the databases were merged into a single file with only combined results reported here. To estimate the impact of complications on healthcare costs and utilization, outcomes were compared between study subjects who had and did not have each complication. Regression models were constructed to estimate the incremental increase in risk of inpatient hospitalization, risk of ED visit, and overall healthcare cost associated with each complication. Demographics, cardiovascular risk factors, presence of complications, and an indicator for the database from which the data were derived were included in the models as independent variables. Logistic regression models were used to estimate risk of inpatient hospitalizations and ED visits. An ordinal least squares (OLS) linear regression analysis was performed for overall healthcare cost. Because cost data is typically skewed, a sensitivity analysis using a Gamma regression was also conducted. Patients had different review years; therefore, all costs were adjusted to 2009 dollars using the medical care component of the Consumer Price Index. All data transformations and statistical analyses were performed using SAS© version 9.2 (SAS Institute, Cary, NC).

Results

We initially identified 3,762 patients with at least one diagnosis of acromegaly between 1/1/02 and 12/31/07 in the PharMetrics database. We selected 1,146 who had either (1) an additional acromegaly diagnosis or, (2) a pituitary tumor. Of these, 771 were continuously enrolled during the calendar year following the first observed acromegaly diagnosis (the year defined as the study period). Similarly, there were 5,719 patients with a diagnosis of acromegaly between 1/1/02 and 12/31/08 in the MarketScan database, of which 1,591 had an additional diagnosis of acromegaly or pituitary tumor, and 1,412 were continuously enrolled in the review period. Combining these data resulted in an initial sample of 2,183 patients. Using an algorithm based on age and visit date, we identified 12 probable duplicate patients (e.g., the same patient appearing in both databases). These patients were randomly removed from one of the databases leaving a final analytic sample of 2,171 unique continuously-enrolled acromegaly patients.

The average age was 45.3 years [standard deviation (SD): 16.1] with a median of 48 years (Table 1). Approximately 50 % (1,080 patients) were female. The majority of patients were from the South (886 patients; 40.8 %) followed by 28.1 % (611) from the Midwest, 17.3 % (375) from the Northeast, and 13.8 % (299) from the West US census regions. The most frequently observed usual-care physician specialties were primary care (family practice, internal medicine, and pediatrics) (778 patients; 35.8 %) and endocrinology (481; 22.2 %). These data indicate that for 35.8 % of patients, 'primary care physician' was listed on the majority of visits, and for 22.2 % of patients, 'endocrinologist' was the specialist listed on the majority of visits.

Many study subjects were presumably diagnosed years prior to the study and would have had surgery or radiation at the time of diagnoses. We had no data on these historical

Table 1 Demographics and usual physician specialty and comorbidity measures in acromegaly patients

	Patient count	Estimate
Mean age in years (SD) [Median]	2,171	45.3 (16.1) [48]
Age categories in years		
<18	186	8.6 %
18–34	245	11.3 %
35–44	430	19.8 %
45–54	624	28.7 %
55–64	593	27.3 %
≥65	93	4.3 %
Female	1,080	49.7 %
Region		
Midwest	611	28.1 %
Northeast	375	17.3 %
South	886	40.8 %
West	299	13.8 %
Usual physician specialty		
Primary care[a]	778	35.8 %
Endocrinology	481	22.2 %
Cardiology	63	2.9 %
Other/unknown[b]	849	39.1 %
Mean number of chronic conditions (SD)	2,171	3.3 (1.8)
Mean Charlson comorbidity index (SD)	2,171	1.0 (1.8)

[a] Including family practice, internal medicine, and pediatrician

[b] No single specialty accounted for >3 % of the "Other" category. Specialty was reported as "unknown" if the relevant data could not be identified on medical claims

Table 2 Acromegaly related tests and treatments during 12 month study period

	Patient count	Percent
Biochemical monitoring tests[a]	1,215	56.0 %
IGF-1	1,166	53.7 %
GH	689	31.7 %
Acromegaly treatment[a]		
Surgery	116	5.3 %
Radiation	50	2.3 %
Pharmacologic treatment	668	30.8 %
Octreotide LAR (long-acting release)	403	18.6 %
Dopamine agonists	213	9.8 %
Octreotide (short-acting)	102	4.7 %
Pegvisomant	89	4.1 %
Lanreotide	27	1.2 %

[a] Patients could have more than one type of test or treatment

IGF-1 Insulin-like growth factor, *GH* growth hormone

treatments, and instead examined treatments received during the one-year study period. In that year, 5.3 % of patients (116) had surgery and 2.3 % (50) had radiation (Table 2). Pharmacologic treatment was used by 30.8 % (668) of patients, with 18.6 % (403) using long-acting octreotide (octreotide-LAR), 9.8 % (213) using dopamine agonists, 4.7 % (102) using short-acting octreotide, 4.1 % (89) using pegvisomant, and 1.2 % (27) using lanreotide. Individual patients could have had more than one type of treatment. Seventy-eight percent (521) of those who received pharmacologic therapy used only one such treatment during the study year, 19.3 % (129) used two, 2.5 % (17) used three, and 0.1 % (1) used 4 types of treatment. Fifty-six percent (1,215) of patients had at least one IGF-1 or GH test during the study year: 53.7 % (1,166) of patients had ≥1 IGF-1 and 31.7 % (689) had ≥1 GH test (Table 2). Among patients receiving pharmacologic treatment, 67.2 % (449/668) had at least one monitoring test.

Complications related to acromegaly were common, with musculoskeletal abnormalities in 25.6 % (556) of patients, hypopituitarism in 16.6 % (361), sleep apnea in 11.5 % (249), cardiovascular abnormalities in 10.3 % (224), reproductive system abnormalities in 9.3 % (201), and colon neoplasms in 6.6 % (143) (Table 3). Cardiovascular risk factors were present in 47.6 % (1,033) of patients: 31.0 % (673) had hypertension, 19.8 % (430) had hypertriglyceridemia, and 17.5 % (379) had diabetes.

Seventeen percent of patients (373) had at least one inpatient hospitalization and 22.9 % (498) had at least one emergency department visit during the study year (Table 4). During the same period, patients had a mean of 16.1 physician office visits (SD: 14.9; median: 12). Mean healthcare costs were $24,900 (SD: $34,129) per patient-year (PPY). Of this total, $17,715 (SD: $30,887) was from medical costs and $7,185 (SD: $14,229) from pharmacy costs. Medical costs were primarily associated with non-emergency department outpatient services (mean: $12,268; SD: $21,185) and inpatient hospitalization (mean: $5,213; SD: $18,611).

In unadjusted comparisons, the presence of any complication was associated with an increase in inpatient hospitalizations (except for reproductive abnormalities, which were associated with a decrease in the proportion hospitalized) ($p < .05$; Table 3). Emergency department visits were more common in patients with cardiovascular disease, with musculoskeletal conditions, and with hypopituitarism than in patients without these conditions ($p < .05$). Similarly, the presence of any of these complications statistically significantly increased costs ($p < .001$) in unadjusted comparisons, except for reproductive system abnormalities. Total annual costs were increased by $18,840 in patients with cardiovascular abnormalities, $16,701 in those with sleep apnea, $14,225 in those with colon neoplasms, $10,989 in those with musculoskeletal abnormalities, and $9,906 in those with hypopituitarism

Table 3 Prevalence of conditions and associated healthcare utilization and cost

		Conditions		Any inpatient hospitalization		Any emergency department visit		Total healthcare cost, $	
		Patient count	Percent	Percent	Difference (%)	Percent	Difference (%)	Mean (SD)	Difference
Condition									
Cardiovascular risk factor									
Diabetes	Yes	379	17.5	26.4	11.2[b]	26.4	4.2	36,321 (42,214)	13,837[b]
	No	1,792	82.5	15.2		22.2		22,484 (31,650)	
Hypertension	Yes	673	31.0	25.4	11.9[b]	30.6	11.1[b]	31,673 (38,524)	9,816[b]
	No	1,498	69.0	13.5		19.5		21,857 (31,501)	
Hypertriglyceridemia	Yes	430	19.8	25.3	10.1[b]	25.1	2.7	28,620 (39,713)	4,639[a]
	No	1,741	80.2	15.2		22.4		23,981 (32,551)	
Acromegaly related complication									
Colon neoplasm[c]	Yes	143	6.6	24.5	7.8[a]	26.6	3.9	$38,188 ($42,559)	14,225[b]
	No	2,028	93.4	16.7		22.7		$23,963 ($33,268)	
Musculoskeletal[d]	Yes	556	25.6	25.9	11.7[b]	31.5	11.5[b]	$33,074 ($39,019)	$10,989[b]
	No	1,615	74.4	14.2		20.0		$22,085 ($31,805)	
Cardiovascular disease[e]	Yes	224	10.3	40.2	25.7[b]	41.1	20.2[b]	$41,796 ($49,607)	$18,840[b]
	No	1,947	89.7	14.5		20.9		$22,956 ($31,309)	
Sleep apnea	Yes	249	11.5	29.3	13.7[b]	27.7	5.4	$39,685 ($45,799)	$16,701[b]
	No	1,922	88.5	15.6		22.3		$22,984 ($31,827)	
Reproductive system abnormality[f]	Yes	201	9.3	16.9	−0.3	25.4	2.7	$22,531 ($29,536)	$-2,610
	No	1,970	90.7	17.2		22.7		$25,141 ($34,561)	
Hypopituitarism	Yes	361	16.6	23.5	7.6[b]	27.4	5.4[a]	$33,158 ($39,177)	$9,906[b]
	No	1,810	83.4	15.9		22.0		$23,25 ($32,794)	

[a] Indicates a statistically significant difference with $p < .05$

[b] Indicates a statistically significant difference with $p < .001$

[c] Colon polyp or colon cancer

[d] Osteoarthritis, arthropathy/arthralgia/synovitis, or carpal tunnel syndrome

[e] Cardiomyopathy, cardiac hypertrophy, heart failure, or cardiac dysrhythmia/arrhythmia

[f] Galactorrhea, menstrual abnormality, impaired libido/impotence, or infertility

compared to those without these conditions. Costs were $2,610 lower in acromegaly patients with reproductive abnormalities than in those without.

In a logistic regression model used to adjust for differences in age, gender, region, and cardiovascular risk factors, having musculoskeletal abnormalities increased the odds of hospitalization (odds ratio [OR]: 1.76; 95 % confidence interval [CI]: 1.36–2.27); as did having cardiovascular abnormalities (OR: 2.93; 95 % CI: 2.12–4.04); and sleep apnea (OR: 1.56; 95 % CI: 1.13–2.17) (Table 5). The odds of an emergency department visit increased with musculoskeletal (OR: 1.87; 95 % CI: 1.48–2.37) and cardiovascular abnormalities (OR: 2.32; 95 % CI: 1.69–3.17). In an OLS linear regression adjusting for the same factors, the presence of acromegaly related complications, except for reproductive system abnormalities, was associated with a statistically significant increase in overall healthcare costs ($p < .01$; Table 5). Costs were increased by $8,401 in patients with colon polyps or colon cancer, by $7,502 in patients with musculoskeletal abnormalities, by $13,331 in those with cardiovascular abnormalities, by $10,453 in those with sleep apnea, and by $6,742 in those with hypopituitarism ($p < .01$). Because cost data are skewed and may violate some assumptions necessary for OLS regression, we conducted sensitivity analyses by repeating all cost models using Gamma regression, which accounts for skewness. These sensitivity analyses confirmed the OLS results.

Discussion

By combining two large health insurance claims databases, we were able to study over 2,000 commercially-insured patients with acromegaly. The data reflect care delivered throughout the US in both inpatient and outpatient settings.

Table 4 Healthcare utilization and costs

	Patient count	Estimate
Inpatient hospitalizations, no.		
0	1,798	82.8 %
1	292	13.5 %
2	51	2.3 %
3+	30	1.4 %
Emergency department (ED) visits, no.		
0	1,673	77.1 %
1	314	14.5 %
2	105	4.8 %
3+	79	3.6 %
Office visits, mean (SD) (Median)	2,171	16.12 (14.9) [12]
Mean total healthcare cost (SD)[a]	2,171	$24,900 ($34,129)
Mean medical cost (SD)	2,171	$17,715 ($30,887)
Inpatient hospitalizations cost	2,171	$5,213 ($18,611)
ED visits cost	2,171	$235 ($946)
Non-ED outpatient services cost	2,171	$12,268 ($21,185)
Mean pharmacy cost (SD)	2,171	$7,185 ($14,229)

[a] All costs from before 2009 were adjusted to 2009 dollars using the medical care component of the Consumer Price Index

To our knowledge, this is the largest study of this rare disease in a broadly representative commercially-insured US population.

In practice, surgery is the most common initial treatment for acromegaly and cures most patients, although for others the disease persists [1, 11]. In this sample of prevalent patients, we studied care delivered over a one year period. In the observation year, just over 5 % of patients had surgery and about half as many received radiation therapy, but many more patients likely had such interventions in prior years. During the study period, 30.8 % of patients received at least one pharmacologic treatment. The majority of these patients likely had prior surgery or radiation therapy and had persistent disease, thus requiring pharmacologic therapy. These results are consistent with an estimate from a recent study of a sample of acromegaly patients in a major US health plan that reported only 28 % received an acromegaly related medication during the study period [12]. In our study, long-acting octreotide and dopamine agonists were the most common pharmacologic therapies, used in 18.6 and 9.8 % of patients, respectively. Short-acting octreotide, pegvisomant and lanreotide were each used by under 5 % of patients. Octreotide was also observed as the most common first pharmacologic treatment in a sample of medically treated acromegaly patients in another study [12]. Treatment guidelines suggest GH or IGF-1 tests should be performed regularly after surgical treatment and during medical therapy to monitor disease activity [13]. If biochemical abnormalities are detected, treatment can be adjusted to achieve control, and evidence suggests that many complications can be prevented, controlled, or reversed with adequate biochemical control [13]. However, only 56 % of patients had one of these tests performed during the year of observation. The lower than expected monitoring rates in this study may indicate that some patients were in remission and so were tested less frequently. In addition, some laboratory tests may not be included in the dataset, either because patients used laboratories outside their payer network and did not send claims to the payer, or because the lab itself failed to submit a claim. Two-thirds of patients receiving pharmacologic treatment had at least one monitoring test during the year. One-fifth of patients had an endocrinologist as their source of usual care, which is another possible indication that the disease was in remission in a large proportion of our sample. However, in the context of claims-based analysis, 22 % of patients having endocrinologists as the usual physician does not mean that the remainder did not visit an endocrinologist during the study year. Rather it means that for this 22 %, an endocrinologist was the specialist listed on the majority of visits.

Complications were common in our study sample. Musculoskeletal abnormalities identified based on claims during the study period were in 25.6 % (556) of patients, hypopituitarism in 16.6 % (361) of patients, sleep apnea in 11.5 % (249) of patients, cardiovascular abnormalities in 10.3 % (224) of patients, reproductive system abnormalities in 9.3 % (201) of patients, and colon neoplasms in 6.6 % (143) of patients. Burton et al. (2012) reported that the highest levels of incidence of comorbidities were found among patients with acromegaly related treatment as compared to those without treatment, which may be in part due to inadequate disease management and suggest the need for earlier diagnosis and treatment, with consistent follow-up care.

Following a model proposed by Ben-Shlomo and colleagues [1], we examined differences in utilization and costs between those acromegaly patients who had, and those who did not have, each of these categories of complications. With this approach, in both unadjusted and adjusted comparisons, we found evidence that complications increase both utilization and cost. The risk of hospitalization was more than 50 % higher in patients with either sleep apnea or musculoskeletal complications than in those without these acromegaly related complications, and nearly three times as high among those with cardiovascular disease as in those without this condition. Furthermore, the presence of five of the six complications (musculoskeletal abnormalities, hypopituitarism, sleep apnea, cardiovascular abnormalities, and colon neoplasms) was associated with an increase in overall cost ($p < 0.05$). The incremental cost of these complications varied from $13,331 for cardiovascular complications to $6,742 for hypopituitarism in

Table 5 Linear regression model of overall healthcare costs and logistic regression models of risk of inpatient hospitalization and risk of emergency department visit

	Overall healthcare costs ($)		Risk of inpatient hospitalization			Risk of emergency department visit		
	Coefficient (SE)	*p*-value	OR	(95 % CI)	*p*-value	OR	(95 % CI)	*p*-value
Age group (in years)								
1–17 versus 65+	4,636 (4,465)	0.299	0.90	(0.42–1.94)	0.789	2.87	(1.54–5.32)	<0.001[a]
18–34 versus 65+	13,431 (4,319)	0.002[a]	1.81	(0.94–3.51)	0.078	1.83	(1.00–3.35)	0.052
35–44 versus 65+	9,334 (4,010)	0.020[a]	1.01	(0.54–1.88)	0.973	1.31	(0.74–2.29)	0.354
45–54 versus 65+	7,807 (3,849)	0.043[a]	0.97	(0.54–1.73)	0.910	0.68	(0.40–1.17)	0.165
55–64 versus 65+	8,683 (3,812)	0.023[a]	0.93	(0.53–1.65)	0.812	0.73	(0.43–1.24)	0.244
Female versus Male	−3,190 (1,427)	0.025[a]	0.87	(0.68–1.11)	0.253	1.35	(1.09–1.68)	0.006[a]
Region								
Midwest versus West	468 (2,319)	0.840	1.09	(0.74–1.59)	0.674	1.41	(0.98–2.02)	0.065
Northeast versus West	−2,762 (2,553)	0.280	0.89	(0.58–1.37)	0.609	1.74	(1.18–2.56)	0.005[a]
South versus West	−8,128 (2,183)	<0.001[a]	0.83	(0.58–1.20)	0.325	1.17	(0.83–1.65)	0.373
MarketScan versus PharMetrics database	2,427 (1,581)	0.125	1.12	(0.86–1.47)	0.400	1.27	(1.00–1.61)	0.053
Cardiovascular risk factor								
Diabetes	10,958 (1,904)	<0.001[a]	1.61	(1.21–2.15)	0.001[a]	1.19	(0.90–1.57)	0.220
Hypertension	4,559 (1,702)	0.007[a]	1.49	(1.13–1.95)	0.004[a]	1.96	(1.52–2..52)	<0.001[a]
Hypertriglyceridemia	208 (1,834)	0.910	1.49	(1.13–1.98)	0.005[a]	1.14	(0.87–1.49)	0.360
Acromegaly related complication								
Colon neoplasm[b]	8,401 (2,858)	0.003[a]	1.11	(0.72–1.71)	0.636	1.08	(0.72–1.64)	0.702
Musculoskeletal[c]	7,502 (1,655)	<0.001[a]	1.76	(1.36–2.27)	<.001[a]	1.87	(1.48–2.37)	<.001[a]
Cardiovascular disease[d]	13,331 (2,405)	<0.001[a]	2.93	(2.12–4.04)	<.001[a]	2.32	(1.69–3.17)	<0.001[a]
Sleep apnea	10,453 (2,254)	<0.001[a]	1.56	(1.13–2.17)	0.008[a]	1.13	(0.81–1.56)	0.473
Reproductive system abnormality[e]	−1,609 (2,475)	0.516	0.95	(0.63–1.45)	0.819	0.99	(0.69–1.41)	0.939
Hypopituitarism	6,742 (1,906)	<0.001[a]	1.31	(0.97–1.75)	0.077	1.31	(1.00–1.73)	0.052

[a] Indicates a statistically significant difference with $p < .05$

[b] Colon polyp or colon cancer

[c] Osteoarthritis, arthropathy/arthralgia/synovitis, or carpal tunnel syndrome

[d] Cardiomyopathy, cardiac hypertrophy, heart failure, or cardiac dysrhythmia/arrhythmia

[e] Galactorrhea, menstrual abnormality, impaired libido/impotence, or infertility

OR Odds Ratio, *CI* Confidence Interval

adjusted analyses (and from $18,840 to $9,906 for these complications in unadjusted comparisons). Reproductive system abnormalities were associated with lower cost in unadjusted comparison, although this difference was not statistically significant after adjustment for confounders. A possible explanation is that infertility may reduce hospitalization for childbirth, the most common reason for hospitalization among US women [14].

Our study estimates the economic burden of acromegaly in the US by totaling payments for treatment of patients with acromegaly, using data from two large claims databases. These data are currently not available from the published literature for US patients with acromegaly. Prior studies used data from outside of the US and reported on older evaluations. In an Italian study conducted in 2004, Didoni et al. [15] reported mean total direct costs for acromegaly cure ranging from 7,968 to 12,533 €/year ($p < 0.01$) for controlled versus inadequately controlled patients. A Canadian study from 1998 presented a longitudinal assessment of economic burden associated with surgical and medical regimens in management of acromegaly, and reported mean annual cost per patient of $8,111 (CAD) [16]. However, these results are likely not applicable to current treatment patterns and costs. Knutzen and Ezzat [17] examined patient survey data from the Pituitary Network Association, and reported estimated annual costs of care after first year of acromegaly diagnosis of $28,435 but did not reference database sources for actual services provided. The authors concluded that overall costs of acromegaly may be considerably higher than may be initially expected, due to the insidious nature of the manifestations of signs and symptoms of this disease and the eventual chronic comorbidities that may result. Our study extends prior research in this area by presenting a more

comprehensive analysis in a recent and large US commercially-insured population, by reporting on economic burden for a large sample of acromegaly patients and providing information specific for the US.

Strengths and limitations

A strength of this study is that it provided detailed claims data on a large sample of acromegaly patients (N = 2,171) through combining two major commercial insurance databases for study of this rare disease. To our knowledge, our study is the first to examine the prevalence of biochemical testing in a US acromegaly population. Similarly, this study is the largest such report on the pharmacologic treatments used in a large group of US patients with this condition. Additionally, for the first time, we have produced age, gender, geographic region, and risk factor adjusted estimates of healthcare utilization and cost of acromegaly related complications using US data. The consistency of our results, both in unadjusted and a variety of adjusted analyses, confirm the robustness of our findings.

Research use of insurance claims data presents unique challenges [18] and our study had limitations. First, to our knowledge, an algorithm for identifying patients with acromegaly using claims has never been validated, although algorithms for identifying various acromegaly cohorts have been previously introduced [12]. We used a common strategy of requiring a confirmatory ICD-9-CM diagnosis (either for acromegaly or pituitary tumor), but it is likely that at least some patients in our sample did not actually have acromegaly and that others with the disease were missed. However, the age distribution, treatments received, utilization and cost observed in our study are consistent with existing literature. Two expert endocrinologists also reviewed the data and concurred that the study population was similar to an acromegaly population that may be seen in clinical practice. Second, this study only included patients with commercial insurance plans that are captured in the two claims databases analyzed in this study, and as a result the geographic distribution of acromegaly patients seen in this study reflects the distribution of plans providing data. In addition, results may not be representative of patients insured by other commercial health plans, uninsured patients, or those with Medicare coverage or other government plans. Third, although we found lower than expected rates of biochemical monitoring in our study, laboratory test results are not reported in this database, so the actual level of biochemical control could not be ascertained. Adjusting for biochemical control would allow patients to be grouped by those whose disease was controlled and those in whom it was not. Future research should examine utilization and cost in patients with active acromegaly compared to those in remission. Fourth, healthcare claims are collected for billing purposes and lack detail about clinical factors, such as disease severity. Therefore, we could not examine the severity of illness for any of the observed complications. Fifth, claims also do not provide historical information; therefore we were unable to examine how long patients had the disease. As a result of these limitations, we are planning a study using primary data collection to extend our research on the typical patterns of treatment. Sixth, although we compared utilization and cost for patients with and without various complications, this study included only patients with acromegaly, therefore, we were not able to compare data on costs or utilization for acromegaly patients versus for patients without acromegaly. Future studies using non-acromegaly controls are also warranted.

Conclusions

Complications, many of which are preventable with adequate therapy, are common and costly in acromegaly patients. Cardiovascular complications nearly tripled the odds of hospitalization (OR 2.93) and increased annual total cost by $13,331. Adequate management of acromegaly may be able to reduce the economic burden associated with these complications and with acromegaly in general.

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References

1. Ben-Shlomo A, Sheppard M, Stephens J, Pulgar S, Melmed S (2011) Clinical, quality of life, and economic value of acromegaly disease control. Pituitary 14(3):284–294
2. Melmed S (2006) Medical progress: acromegaly. N Engl J Med 355(24):2558–2573
3. Chanson P, Salenave S, Kamenicky P et al (2009) Acromegaly. Best Pract Res Clin Endocrinol Metab 23(5):555–574
4. Dekkers O, Biermasz N, Pereira A, Romijn J, Vandenbroucke J (2008) Mortality in acromegaly: a metaanalysis. J Clin Endocrinol Metab 93(1):61–67
5. Colao A, Ferone D, Marzullo P, Lombardi G (2004) Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev 25(1):102–152
6. O'Malley A, Pham H, Schrag D, Wu B, Bach P (2007) Potentially avoidable hospitalizations for COPD and pneumonia: the role of physician and practice characteristics. Med Care 45:562–570

7. Agency for Healthcare Research and Quality (AHRQ): HCUP Chronic Condition Indicator. Healthcare Cost and Utilization Project (HCUP). AHRQ. www.hcup-us.ahrq.gov/toolssoftware/chronic/chronic.jsp. Accessed 5 Sep 2012
8. Hwang W, Heller W, Ireys H, Anderson G (2001) Out-of-pocket medical spending for care of chronic conditions. Health Aff 20:267–278
9. Charlson M, Pompei P, Ales K, MacKenzie C (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5): 373–383
10. Deyo RA, Cherkin DC, Ciol MA (1992) Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 45(6):613–619
11. Ezzat S, Serri O, Chik CL et al (2006) Canadian consensus guidelines for the diagnosis and management of acromegaly. Clin Invest Med 29(1):29–39
12. Burton T, Le Nestour E, Bancroft T, Neary M (2013) Real-world comorbidities and treatment patterns of patients with acromegaly in two large US health plan databases. Pituitary 16(3):354–362
13. Katznelson L, Atkinson J, Cook D, Ezzat S, Hamrahian A, Miller K (2011) AACE Acromegaly Task Force. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Acromegaly—2011 update. Endocr Pract 17(4):1–44
14. Wier L, Pfuntner A, Maeda J, Stranges E, Ryan K, Jagadish P, Collins Sharp B, Elixhauser A (2011) HCUP facts and figures: statistics on hospital-based care in the United States, 2009. Agency for Healthcare Research and Quality. http://www.hcup-us.ahrq.gov/reports.jsp. Accessed 17 Oct 2012
15. Didoni G, Grottol S, Gasco V et al (2004) Cost-of-illness study in acromegalic patients in Italy. J Endocrinol Invest 27(11): 1034–1039
16. Wilson L, Shin J, Ezzat S (2001) Longitudinal assessment of economic burden and clinical outcomes in acromegaly. Endocr Pract 7(3):170–180
17. Knutzen R, Ezzat S (2006) The cost of medical care for the acromegalic patient. Neuroendocrinology 83:139–144
18. Tyree P, Lind B, Lafferty W (2006) Challenges of using medical insurance claims data for utilization analysis. Am J Med Qual 21(4):269–275