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ORIGINAL ARTICLE

Use of administrative health databases to estimate incidence and prevalence of acromegaly in Piedmont Region, Italy

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Abstract

Purpose Recent studies from national registries have described changing patterns in epidemiology of acromegaly. Our retrospective study used administrative databases to estimate prevalence and incidence of acromegaly in the Piedmont Region, Italy.

Methods This study was conducted in Piedmont between 2012 and 2016 on administrative health databases for inpatients and outpatients of any age. Enrollees were included if claims suggestive of acromegaly were identified in at least two of the following databases: Drug Claims Registry, Hospital Information System, Co-payment Exemption Registry and Outpatient Specialist Service Information System.

Results 369 individuals (M = 146, F = 223) met our criteria. Overall incidence was 5.3 per million person years (95% CI 4.2–6.7), and prevalence was 83 cases per million inhabitants (95% CI 75–92). Mean age was 50.9 years. Both incidence and prevalence were slightly higher among women (rate ratio 1.08, prevalence ratio 1.43). Age-specific incidence was similar between sexes up to 39 years and diverged thereafter, with an increasing trend recorded among men. Prevalence was higher in women aged 40–79 years, and increased continuously up to 79 years in both sexes.

Conclusions This is the first population-based study conducted in Italy to estimate incidence and prevalence of acromegaly and results show a higher prevalence than previously reported. Although our algorithm requires proper validation, it constitutes a promising tool to describe the epidemiology of acromegaly.

Keywords Acromegaly · Algorithm · Incidence · Prevalence · Administrative health databases

Introduction

Acromegaly is a rare entity resulting from a growth hormone (GH)-secreting pituitary adenoma [1]. The presentation and initial diagnosis of acromegaly can be insidious and, despite the advances in this field, there are significant diagnostic delays that could prompt adverse sequelae and influence the long-term disease prognosis. Hence, a timely diagnosis is desirable. To increase awareness on the disease, the Endocrine Society guidelines advised to screen for acromegaly in patients with typical clinical manifestations as well as in those without somatic signs but who carry several typical comorbidities of acromegaly, such as obstructive sleep apnea, type 2 diabetes mellitus, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis, and arterial hypertension [2]. Similar recommendations were issued in the American Association of Clinical Endocrinologists (AACE) guidelines [3]. Another relevant issue is represented by therapeutic millstones. GH-secreting pituitary tumors display a high prevalence of macroadenomas, which reduces the likelihood of complete surgical cure and prompts persistent disease in over 60% of cases [4–7]. In such instances, multimodal therapies are necessary. Because these diagnostic and prognostic factors impact on the health care systems, it is important that optimal knowledge exists on chronic care activities related to acromegaly, including epidemiology, therapeutics and practices.

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Most epidemiological data currently available are extracted from data collected in specialized referral centers, whose catchment areas may not cover the whole population. Published estimates have suggested highly variable figures encompassing prevalence rates of 28–137 cases per million and annual incidence rates of 2–12 cases per million person years [3, 6, 8–15]. To improve accurateness in describing the epidemiology of acromegaly and its impact on healthcare systems [15], recent US studies have employed a novel analytical approach to derive estimates of incidence and prevalence based on data from population healthcare databases and insurance claims [13, 16, 17]. These recent epidemiological data collectively suggest that incidence and prevalence of acromegaly are rising [13, 17]. Uncertainty remains on whether this is the result of improved diagnostic tools, stricter clinical surveillance or temporal changes in incidence rates. The aim of our study was to estimate the prevalence and incidence of acromegaly in the Piedmont Region (Italy) through the analysis of routinely collected administrative data.

Methods

Data source

A retrospective cohort study was conducted using the Administrative Health Databases (AHDs) of Piedmont Region (about 4,400,000 inhabitants, corresponding to 7.5% of the national population), from January 1, 2012 to December 31, 2016. Only data regarding patients residing in Piedmont were considered by employing a combined strategy encompassing fiscal and health-related residential categories. Data were obtained from four different databases: (a) Drug Claims Registry, including records of all outpatient drug prescriptions reimbursable by the National Health Service (NHS); (b) Hospital Information System, including records of all hospital discharge forms (HDFs) from public or private hospitals; (c) Co-payment Exemption Registry; (d) Outpatient Specialist Service Information System, reporting records of endocrine visits and healthcare services related to the workup of acromegaly provided by the NHS (laboratory and medical tests, outpatient visits, neuroimaging). These four databases can be linked through a unique identifier, which remains unchanged over time. The medical claims in HDFs included information on diagnoses reported according to the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) diagnosis codes. Laboratory and radiological data included information reported according to the *National Tariff Nomenclature* (NTN) codes.

Selection of cases

Potential cases were defined as the subjects who had claims suggestive of acromegaly in at least two of the four databases during the study period. The claims taken into account were:

1. Hospital discharge records with an acromegaly diagnosis code (ICD-9-CM: 253.0);
2. Exemptions from co-payment for acromegaly (code: 001);
3. Prescriptions for any of the following medications: octreotide (ATC: H01CB02), lanreotide (ATC: H01CB03), pegvisomant (ATC: H01AX01), pasireotide (ATC: H01CB05);
4. Prescriptions for any of the following radiological tests: facial bone nuclear magnetic resonance (NMR) (codes 88.91.3–88.91.4); cranial (sella turcica, orbit) computed tomography (CT) (codes 87.03–87.03.1).

To further improve the specificity of our approach, we did not take into considerations drug prescriptions if:

1. Patients had received less than three separate drug prescriptions for the treatment of acromegaly (occasional drug users);
2. The medications were not long-acting release (LAR) formulations;
3. Patients taking octreotide or lanreotide had a hospitalization with a diagnosis different from acromegaly, among those for which there is an indication for the use these drugs, as reported in the summary of product characteristics (malignant neoplasms (ICD-9: 140–209, 230–239), liver disorders (ICD-9: 570–573), gastrointestinal bleeding (ICD-9: 578), esophageal varices (ICD-9: 42), Cushing's disease (ICD-9: 255; 255.0)
4. Patients had an exemption from co-payment for Cushing's disease (code: 032).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the local ethical committee of the "Maggiore della Carità" Hospital, Novara (CE 58/18). The study was performed using data routinely collected in the regional administrative health care databases and the authors had access only to anonymized data, so for this type of study informed consent was not required.

Statistical analysis

Prevalence was calculated by dividing the number of prevalent cases of acromegaly (i.e., those with acromegaly-related claims at any time during the period 2012–2016) by the total number of residents in Piedmont. Incidence was calculated by dividing the number of new acromegaly cases (i.e., no evidence of acromegaly during the 2 years prior to the index claim) by the size of the population total time at risk during the period 2014–2016. Incidence and prevalence estimates were stratified by age (≤ 19, 20–39, 40–59, 60–79, and ≥ 80 years) and sex. Comparisons of incidence and prevalence between the two sexes were carried out estimating rate ratios and prevalence ratios. Analyses were performed with the software Stata 12 (StataCorp, College Station, TX, USA).

Results

In the period 2012–2016, we found 369 individuals in the Piedmont population, 146 males and 223 females, who met our combined criteria for diagnosis of acromegaly. Incident cases in the period 2014–2016 were 71, of whom 33 were men and 38 were women. Mean age was 50.9 years. The observed number of cases translated into an incidence of 5.3 per million per person years (95% CI 4.2–6.7) and a prevalence of 83 per million inhabitants (95% CI 75–92) (Table 1). When the index cases were stratified by sex, both the incidence and the prevalence were slightly higher among women. Compared to men, the rate ratio of women was 1.08 (95% CI 0.67–1.72), while the prevalence ratio was 1.43 (95% CI 1.16–1.76). Incidence rates were lowest among subjects with less than 19 years old. Age-specific incidence rates were similar in the two sexes up to the age of 39 years but seemed to diverge thereafter, with an increasing trend recorded among men compared to women (Fig. 1). Prevalence increased in both sexes continuously up to 79 years of age, and markedly decreased thereafter. Prevalence of acromegaly was substantially higher in women than men between 40 and 80 years of age (Fig. 2).

Table 1 Prevalence (period 2012–2016) and incidence (period 2014–2016) of acromegaly in Piedmont Region (Italy), stratified by sex

	Men		Women	
	N	Point estimate (95% CI)	*N*	Point estimate (95% CI)
Incidence	33	5.1 (3.6–7.2)	38	5.5 (4.0–7.6)
Prevalence	146	68 (58–80)	223	97 (85–111)

Results expressed as cases per million person years (incidence) and cases per million inhabitants (prevalence)

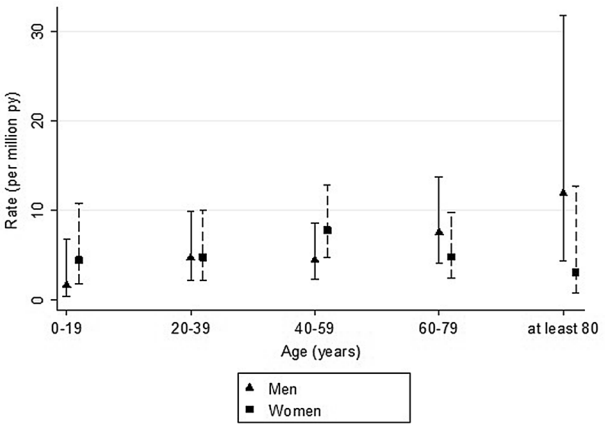

Fig. 1 Incidence of acromegaly in Piedmont Region (Italy) in the period 2014–2016, stratified by sex and age groups

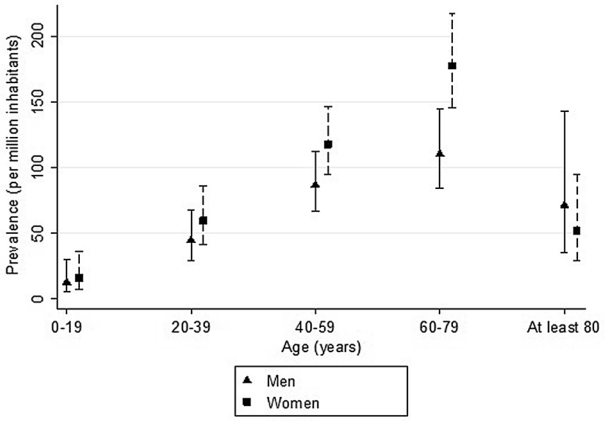

Fig. 2 Prevalence of acromegaly in Piedmont Region (Italy) in the period 2012–2016, stratified by sex and age groups

Discussion

This is the first population-based study conducted in Italy to estimate the prevalence and incidence of acromegaly in a geographically defined population, without the apparent limitations related to catchment area and referral practice. To do so, we developed an algorithm that identifies acromegaly cases combining information from four different administrative databases. This approach is similar to that adopted by Burton et al. [13] and Broder et al. [17], who used two large health insurance databases to estimate the incidence of acromegaly in the US. In addition to medical and pharmacy claims, however, our algorithm takes also advantage from information included in the Co-payment Exemption Registry and in the Hospital Information System, two reliable sources of data that have been previously used for epidemiological

research in Italy. Our study showed an overall incidence of acromegaly of 5.3 cases per million person years, while the prevalence was 83 cases per million inhabitants. While the incidence of acromegaly here reported is comprised within the highly variable range of 1.9–7.7 cases per million person years found in European studies [9, 14, 18–24], two recent US surveys have reported an even higher incidence rate, corresponding to 9.6–11.7 cases per million person years [13, 17]. The discrepancy of the results between the US and the European surveys could be due both to differences in study methodologies and to real differences in the incidence of the disease across the world. Mean age at the diagnosis of acromegaly in our study was 50.9 years and we observed an increasing trend of incidence with age, which is aligned with recent reports [15]. Although the overall incidence was similar between sexes, an age-specific analysis showed that trends of incidence were similar between sexes up to the age of 39 years but slightly increased in men thereafter, compared to women. These results are consistent with those obtained in the Swedish Pituitary Registry, which displayed an increasing trend for men and a decreasing one for women after the age of 35 years [21].

With regard to prevalence, we observed an increase with age in both sexes, leading to a peak in the age group 60–79 years. Prevalence was higher in women than in men up to the age of 80 years, whereas the opposite was documented thereafter. The prevalence of 83 cases per million inhabitants found herein is higher than that of 60 cases per million recorded in a large Italian survey [25], as well as that obtained in past European studies [4, 19]. However, our estimates parallel the prevalence rates documented in more recent surveys [13, 14, 17]. Interestingly, an Icelandic survey found an even higher prevalence for acromegaly, reaching 121 cases per million inhabitants [23]. It is still a matter of debate whether incidence rates of acromegaly are increasing over time, and whether this is a real phenomenon or it is rather attributable to improved diagnostic techniques and disease awareness. Likely, the development of sensitive immunoassays for measuring GH and IGF-1 levels, as well as the widespread use of MRI for detecting small pituitary tumors, has increased the number of diagnoses of acromegaly over time [26]. In fact, many of the earlier studies were performed when neuroimaging technology could only allow the identification of large tumors, while highest resolution and vast use of MRI now enables identification of pituitary masses that, previously, would have been too small to detect [27]. For this reason, incidentally discovered pituitary mass can be now identified in patients undergoing neuroimaging for unexplained headache, head injury workup, sinus disease, cervical spine disease, and vertigo. Once the diagnosis of pituitary mass is made, clinical evaluation often includes complete assessment of pituitary function to uncover an otherwise clinically silent disease [28]. Also, current diagnostic criteria could have contributed to the increase of incidental diagnosis of acromegaly, as they no longer require the presence of typical phenotypic features of acromegaly [2]; moreover, in recent series no visible pituitary tumor on MRI was found, but the presence of GH-secreting pituitary adenoma of very small dimension was confirmed post-surgical exploration [29]. Finally, increased awareness of the condition and its early manifestations may also have contributed to the apparent increase in disease prevalence.

Population-based design, definite regional enrollment, and multiple database sources are major strengths of our study. Results from this type of epidemiologic study are more generalizable than estimates derived from single-institution studies or case series [15], and could partially compensate for the lack of national registries. Moreover, our study included all age groups, compared to other studies, capturing only commercially-insured patients under the age of 65 years [17]. A limitation of using claims data to estimate disease incidence is the inability to know with certainty that the first claim observed in the data corresponds to the first clinical diagnosis of the condition. Moreover, this approach cannot provide information on time from clinical diagnosis and disease status (e.g., active vs. inactive disease), as well as it lacks information on adenoma size, hormone levels, clinical stratification of subgroups, and cases of multiple endocrine neoplasia-1. Another potential limitation of the present study is the apparently short period of observation (2012–2016). However, similar time-confined methodologies have been employed for epidemiology purposes in other acromegaly-related studies [13, 17], and are reckoned to appropriately reflect average epidemiology of the disease. Finally, but more importantly, our algorithm requires validation to constitute an effective tool.

In conclusion, this study provides a novel method to estimate the incidence and prevalence of acromegaly in the general population. Our results are consistent with the available literature on this topic and show a higher prevalence of acromegaly than previously reported. Even if our algorithm still requires proper validation, it represents a promising tool to describe the epidemiology of acromegaly, to assess its burden on patients and health care systems, and to provide guidance on resources allocation, especially in countries lacking national registries of acromegaly. Future developments include the assessment of time trends of the disease and the extension of the study to other Italian regions to evaluate the geographical heterogeneity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the local ethical committee of the "Maggiore della Carità" Hospital, Novara (CE 58/18).

Informed consent The study was performed using data routinely collected in the regional administrative health care databases and the authors had access only to anonymized data, so for this type of study informed consent was not required.

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