Pituitary (2015) 18:803–807
DOI 10.1007/s11102-015-0655-4

The incidence and prevalence of acromegaly, a nationwide study from 1955 through 2013

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Published online: 17 April 2015

Abstract
Context Acromegaly is a rare disease with complications and increased mortality. The incidence and prevalence of acromegaly worldwide is not well known.
Objective To gather information on patients diagnosed with acromegly in Iceland over 59 years.
Design Information was retrospectively gathered about patients diagnosed with acromegaly from 1955 through 2013. Incidence was calculated from the total Icelandic population.
Setting/patients Information was gathered from medical records at Landspitali National University Hospital, Iceland, housing the only endocrine department in the country, at the largest hospital outside of Reykjavik (Sjúkrahúsið á Akureyri, Akureyri Hospital) and the largest private outpatient clinic in Reykjavik, where some of the patients received follow-up care. Further, information on patients were sought from all endocrinologists treating adult patients in Iceland. All patients diagnosed with acromegaly during the study period were included.
Results Fifty-two patients (32 men) were diagnosed during the study period. The average age at diagnosis was 44.5 years. Nine patients had died. Symptoms had been present for more than 3 years in most cases. Twenty-five patients had hypertension (48 %). Follow up information was available for 48 patients, 63 % were considered cured after treatment.
Conclusions The incidence of acromegaly in Iceland during the study period was much higher than earlier reports have indicated. During the last 9 years of the study 7.7 patients were diagnosed per million per year. At diagnosis, 38 % had developed hypertension and 10 % were diagnosed during follow up. This indicates the importance of endocrine disorders in the aetiology of hypertension.

Keywords Acromegaly · Growth hormone · Pituitary tumor · Hypertension

Introduction

Acromegaly is a rare disease. The incidence and prevalence of this syndrome are not well known worldwide. Published prevalence numbers have been between 40 and 70 cases/million inhabitants and the incidence rate 3–4 cases/million inhabitants/year [1–3]. A few published reports have shown higher numbers as Daly et al. [4] that described a prevalence of 12 cases per 100,000 population in a cross sectional study from Belgium in 2005. The average age at diagnosis has been described around 46 years and the frequency is similar for both genders [3]. The incidence and prevalence in Iceland is currently unknown.

The effect of increased production of growth hormone (GH) on many organs is well known and serious complications of acromegaly include hypertension, heart disease, diabetes and sleep apnoea [5–7]. Mortality is 2–3 times higher than in the general population, stressing the need to diagnose the disease as early as possible [8].

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The diagnostic methods and treatment for acromegaly have changed immensly in the last 25 years. Despite these changes, there is a significant diagnostic delay (time from start of the disease to diagnosis) and patients commonly have severe symptoms and complications by the time they are diagnosed and receive treatment. It has been reported that symptoms have been present for an average of 7–10 years at diagnosis [3].

The aim of this study was to gather information on patients diagnosed with acromegaly in Iceland from 1955 through 2013. There is only one University Hospital in Iceland, [Landspítali National University Hospital (LSH)], which houses the only endocrinological ward where diagnosis of acromegaly is made. These unique circumstances makes it realistic to believe that all patients that have been diagnosed during the research period are included in the study making the incidence and prevalence numbers accurate.

Materials and methods

Subjects

In this retrospective study, information was gathered about all patients diagnosed with acromegaly in Iceland from the year 1955 through 2013. The incidence was calculated from the total icelandic population during those years (Hagstofa Íslands, Statistics Iceland). Information on patients with pituitary adenomas diagnosed from 1955 until 2007 had already been gathered and imported into electrical patient journals at LSH [9]. Additional information was gathered by searching for the diagnosis af acromegaly [E22.0 according to the International Classification of Diseases, 10th edition (ICD-10)] in medical records at LSH, at Akureyri Hospital (Sjúkrahúsið á Akureyri) the largest hospital out of the capital and at Laeknasetur, the largest outpatient private clinic in Iceland, where some patients received follow-up care. All consulting endocrinologists in Iceland provided further information on patients with acromegaly in their care. No additional patient was found through contact with these endocrinologist, every patient included in the study was found through search of the patient journals at LSH.

Approval for the study was obtained from The Data Protection Authority, (2010111089ÞS/-) The National Bioethics Commitee (VSNb2010110031/03.1) and Chief Medical Excecutive of LSH, all in Iceland.

All patients were diagnosed according to accepted criteria at each time. Clinical signs and symptoms were documented as well as methods used to confirm the diagnosis. X-ray was initially used to examine the sella turcica, thereafter computed tomography (CT) and then magnetic resonance imaging (MRI), the standard objective method today. After surgery tumor tissue was sent for histopathological diagnosis (PAD).

Results

Subjects

Fifty-two patients (n = 52, 32 men) were diagnosed with acromegaly during the study period (Table 1). The average age at diagnosis was 44.5 years. Nine patients had died. The prevalence of acromegaly in Iceland in 2013 was 133 cases per million inhabitants when only patients that had died were subtracted but 121 cases per million inhabitants when patients that were lost to follow up were subtracted as well.

Symptoms and comorbidities

Symptoms had been present for more than 3 years in most cases but in three cases for at least 15 years. The most common symptoms at presentation were enlargement of hands and feet as well as changes in facial features (Table 2), 25 patients had hypertension (48 %), 7 had diabetes (13 %), 10 had decreased glucose tolerance (19 %), 5 had heart failure (10 %) and 4 had coronary artery disease (8 %). Of the 25 patients with hypertension, 20 were diagnosed before the diagnosis of acromegaly, an additional three patients had borderline hypertension at diagnosis which evolved to hypertension and two patients were diagnosed later. Three patients with hypertension and two with diabetes did not need medical treatment for these comorbidites after surgical removal of the pituitary tumor.

Hormone measurements, objective research and PAD

Serum GH measurements were done at diagnosis for all patients except one. GH curves were documented as part of the workup during the last 4 years of the study and were available for 21 patients (40 %). Glucose tolerence tests were available for 42 patients (81 %). Serum measurements of insulin like growth factor 1 (IGF-1) or Somatomedin C were available for 33 patients (63 %) Blood pressure measurements at diagnosis were available for 48 patients (92 %). MRI results were available for 34 patients (65 %), CT results for 10 patients (19 %) and X-ray results for 6 patients (12 %). Thirty-seven patients had confirmed macroadenomas (71 %), 10 patients had microadenomas (19 %) but information for the size of the tumor was missing for five patients. Histopathological results confirmed adenoma tumors for 39 patients (75 %),

Table 1 The prevalence and mortality of acromegaly in Iceland through 1955–2013

	Number of patients	Mean age at diagnosis (range)	Icelandic population mean (range)	Patients per million/year	Patients dead	Mortality in Icelandic population
1955–1964	2	24.5 (15–34)	171,842 (156,033–187,314)	1.16	0	1211
1965–1974	3	50.7 (27–64)	202,564 (190,652–213,722)	1.48	0	1428
1975–1984	7	44.7 (25–72)	226,649 (216,695–238,416)	3.09	1	1511
1985–1994	11	36.0 (5–63)	252,327 (240,606–265,064)	4.36	4	1720
1995–2004	7	44.7 (24–61)	273,093 (266,978–293,577)	2.56	1	1839
2005–2013	22	49.7 (23–76)	316,075 (293,577–321,857)	7.7	3	1955
Total	52				9	

Table 2 Most common symptoms at presentation

Enlargement of hands/feet	41	Visual disturbances	18
Change of facial bones	37	Mandibular prognathism	15
Headache	29	Decreased libido/impotence/amenorrhea	14
Joint pain	26	Thickening of lips	13
Enlargement of nose	25	Increased gap between teeth	12
Macroglossia	24	Disturbance of peripheral vision	10
Diaphoresis	23	Hirsutism	8
Thickening of skin	20	Weight increase	9
Fatigue	20	Deepening of voice	9

immunohistochemical staining demonstrated GH within the cell cytoplasm in 36 samples (69 %) but further analysis was missing for the three remaining patients.

Other measurements at diagnosis were serum levels of cholesterol, triglycerides, low density lipoproteins, TSH, fT4, fT3, testosterone, prolactin, cortisol, luteinizing hormone and follicule stimulating hormone. Common additions to the work up were chest X-rays, electrocardiograms and cardiac ultrasounds.

Treatment

Surgical operations to remove the tumor were performed on 40 patients (77 %), 34 of which were performed in Iceland, five in a Scandinavian country, one in the United States and one in Australia. For 37 patients (71 %) surgery was the first choice of treatment, the three (6 %) remaining patients had tried pharmacological treatment with somatostatin analogs prior to surgery without an acceptable remission. For these three patients treatment with somatostatin analogs was initiated to reduce tumor size before surgery, for one patient (2 %) surgery was not anticipated to be successful. In one of these three cases the patient refused surgery until pharmacological treatment was unsuccessful. Ten patients had two operations (19 %) and three patients had three operations (6 %). Two patients had four operations (4 %) one patient had five (2 %), without secure cure. These two patients had not been cured at the end of the study period. Twenty-six patients had pharmacological treatment (50 %), either as the main treatment or combined with surgical treatment, 12 patients with Dopamine Receptor Agonists (DRI), 10 patients with GH Inhibitors (GHI), and 4 patients with both DRI and GHI). Other treatment choices were conventional radiation therapy (14 patients, 27 %) and treatment with gammaknife (3 patients, 6 %).

Cure rate

Follow up information was available for 48 patients (92 %), four patients were lost to follow up after having moved out of the country. Out of the 44 patients that were left, 30 patients (68 %) were considered cured of their disease after treatment. Overall cure rate was 60 %. Eighteen patients had not been cured when these data were collected.

Discussion

In this study we found 52 patients with acromegaly diagnosed during a period of 59 years. Thus, the incidence for acromegaly was much higher than earlier reported [1–3]. During the last 8 years of the study period, 7.7 patients were diagnosed per million per year (0.77 per 100,000 per year) which is approximately two times higher than earlier

reports (3–4 cases per million per year). The prevalance in 2013 was also much higher than previously reported, 134 cases/million inhabitants. Iceland gives a unique opportunity to gather information on rare diseases as acromegaly, and in view of the high incidence we found, it would be of great interest to see similar studies performed in other countries.

Interestingly 38 % of the patient population had developed hypertension at the time they were diagnosed with acromegaly, and an additional 10 % were diagnosed later, indicating the importance of endocrine disorders, here acromegaly, in the aetiology of hypertension. Seventeen patients had decreased glucose tolerance, seven of which had confirmed diabetes at diagnosis of acromegaly. All of the patients with diabetes and all but one with decreased glucose tolerance had hypertension as well. Three patients with hypertension and two with diabetes did not need medication after treatment of acromegaly which stresses the importance of early diagnosis in order to reduce comborbidities. Unfortunately serum lipid measurements were missing for many patients so no definite conclusions could be made on the connection between acromegaly and hyperlipidemia. Heart failure was diagnosed in 10 % of the patients at diagnosis and 8 % had confirmed coronary artery disease. Thus, variables connected to increased cardiovascular morbidity and mortality were usual in the study population.

The high incidence of acromegaly in Iceland can be speculated on. Evolvement of diagnostic tools and treatment choices, both pharmacological and surgical, may lead to increased alertness of the disease and this could increase diagnostic rates of acromegaly. The proximity of specialist services in the country, for other doctors and for the patient might increase the possibility of a correct diagnosis of complicated, rare diseases. Considering the vast comorbidities and wide spectrum of symptoms, it is important to reduce diagnostic delay. Thus, doctors need to be alert for acromegaly in their daily practice. With advances in microsurgery with the aid of navigation technique and a broad spectrum of other treatment options, the aim of diagnosis should be to cure the disease. Reported cure rates have been between 42 and 70 % depending mostly on the size of the tumors with the results being better for smaller tumors in comparison with larger tumors [10]. This is similiar to our findings of an overall cure rate of 63 or 68 % excluding the four patients lost to follow up.

In an article from 2006, a research group from Finland introduced a germline mutation in the aryl hydrocarbon receptor interacting protein (AIP) gene in individuals with pitutary adenoma predisposition in a population-based study from northern Finland [11]. The group had found three clusters of familal pituitary adenomas and showed that two AIP mutations accounted for 40 % of patients in their study group that were diagnosed with GH secreting pituitary adenomas before the age of 35 and 16 % of all the patients. In our compilation of patients with acromegaly in Iceland diagnosed during the period 1955–2013, questions were also raised about the genetics of the disease since two of our patients were brothers and two other patients were closely related.

We conclude that the incidence and prevalence of acromegaly in Iceland is higher than earlier reported and hypertension was the most common comorbidity. The high incidence and prevalence found in this study stresses the need of further studies from other countries on the subject. The question regarding the genetics of the disease remains a point for further investigation.

Acknowledgments We thank our collegues, for excellent collaboration in supplying clinical information on their patients from their private praxis. This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Conflict of interest None.

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