Changes in the management and comorbidities of acromegaly over three decades: the French Acromegaly Registry

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Abstract

Context: Acromegaly is a rare disease associated with chronic multisystem complications. National registries have been created in several countries.

Design: The French Registry contains data on acromegaly epidemiology, management and comorbidities recorded over more than three decades, retrospectively until 1999 and prospectively from 1999 to 2012.

Results: Data could be analyzed for 999 of the 1034 patients included in the registry (46% males). Disease control, defined as IGF-I normalization (adjusted for age and sex), was achieved in 75% of patients at the last follow-up visit. Half the patients with uncontrolled disease had IGF-I levels below 1.5 times the upper limit of normal (ULN). The proportion of patients with surgically cured disease did not change markedly over time, whereas the proportion of patients with uncontrolled disease fell and the proportion of patients with medically controlled disease rose. Cardiovascular, metabolic, respiratory and rheumatologic comorbidities and their outcomes were recorded for most patients, and no noteworthy overall deterioration was noted over time. Cancer occurred in 10% of patients, for a standardized incidence ratio of 1.34 (95% CI: 0.94–1.87) in men and 1.24 (0.77–1.73) in women. Forty-one patients died during follow-up, for a standardized mortality ratio of 1.05 (0.70–1.42). Most deaths were due to cancer.

Conclusions: The majority of patients with acromegaly now have successful disease control thanks to the multistep management. The incidence of comorbidities following diagnosis of acromegaly is very low. Life expectancy is now close to that of the general population, probably owing to better management of the GH/IGF-I excess and comorbidities.

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Introduction

Acromegaly is a chronic systemic disease caused by growth hormone (GH)-secreting pituitary adenomas. It is associated with increased morbidity, impaired quality of life and reduced life expectancy, primarily because of cardiovascular disease and cancer (1, 2, 3). Management of acromegaly has changed in recent decades, with the advent of new medical therapies and the use of more stringent criteria for disease control (4, 5, 6). The need for epidemiological data, and the rarity of acromegaly, prompted the creation of several national registries (7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22). The French Acromegaly Registry was created in 1999 by the French Pituitary Club, a working group of the French Society of Endocrinology. It collects data from centers located throughout France and also from French-speaking areas of Switzerland and Belgium. The data were collected both retrospectively (clinical and biological data for 332 patients from 1977 to 1999 and onward) and prospectively (for 702 patients from 1999 to 2012).

The registry was designed to collect real-life clinical, biochemical and morphological data, principally to analyze patient management. Thus, all recorded biochemical data came from routine testing in each participating center, without central analysis. Clinical and biochemical data for each patient were recorded during serial visits, allowing us to analyze trends in disease control and comorbidities over a period spanning more than three decades.

Methods

Data collection and management

All participating centers and their local ethics committees signed a confidentiality agreement. Each patient provided written informed consent to participate in the registry. Thirty-three centers effectively contributed data to the registry. [Supplementary Figure 1](#) (see section on [supplementary data](#) given at the end of this article) shows the geographic locations and recruitment of the participating centers. Each patient was identified by a unique alphanumeric code. Data were recorded and stored in a local server in each participating center. A software program was designed by members of the French Pituitary Club and developed by PC-PAL (Wissous, France). All available data were pooled and exported for statistical analysis.

The following information was recorded for each patient: date of birth and gender, body mass index (BMI), the estimated duration of acromegaly, and, at each visit, acromegaly control status, defined as (1) uncontrolled, when the IGF-I levels is above the ULN for age and sex, as measured locally; (2) controlled, when the IGF-I level is normal on medical treatment, or less than 6 months off treatment and (3) cured, when the IGF-I level is normal, off treatment, for more than 6 months. Other collected information included pituitary tumor size and extension, as determined by magnetic resonance imaging (MRI), the type and date of neurosurgery, radiotherapy (RT) and medical treatments (MTs).

At inclusion, as well as postoperatively and at each visit, the following parameters were recorded: the mean plasma GH (GH basal profile on at least 3 samples, every 15 or 30 min and nadir after oral glucose tolerance test (OGTT)) and the IGF-I level (expressed either as the absolute level or as the percentage above the upper limit of normal (ULN) for age and sex), the lipid profile, fasting glucose, HbA1C and systolic and diastolic blood pressure. The following comorbidities were recorded: (1) cardiac: hypertension, valve disease, arrhythmias, myocardial hypertrophy (indexed left ventricular mass and Devereux formula), heart failure and coronary artery disease; (2) vascular disease and cerebrovascular events; (3) type 2 diabetes mellitus (T2DM, according to the WHO 1999 criteria); (4) respiratory disorders: obstructive sleep apnea (OSA) and respiratory failure; (5) rheumatologic diseases: joint pain, carpal tunnel syndrome and hip osteoarthropathy; (6) colonic polyps; (7) anterior pituitary deficiencies: any type, gonadotropic, corticotropic and thyrotropic; (8) headache and visual defects and (9) cancers (type and site).

Statistical analysis

Data for individual patients were exported to multiple Microsoft Excel databases. In Tables and Figures, descriptive statistics are shown as medians with interquartile ranges or individual values for continuous variables, or as proportions for categorical variables, as appropriate. All-cause mortality was compared with that of the French population by calculating the standardized mortality ratio (SMR), which is the ratio between the observed number of deaths in the study sample and the expected number of deaths according to the French

National Institute of Statistics (INSEE, <http://www.insee.fr>). Similarly, the incidence of cancer was compared with French population data by calculating the standardized incidence ratio (SIR), which is the ratio between the number of cancers observed in the study sample and the expected number of cancers according to the French National Cancer Institute (<http://www.e-cancer.fr>). Paired or unpaired non-parametric *t*-tests were used to compare continuous variables, as appropriate. The chi-square test and Fisher's exact test were used to compare categorical data. The Spearman's rank test was applied to define correlations. The individual effect of each demographic, clinical and biochemical variable as predictors of cardiovascular, cerebrovascular, metabolic, respiratory, rheumatologic, neoplastic, pituitary deficiency as well as of treatment outcomes was evaluated using a multiple logistic regression model. To limit confounding factors, the study design included adjustment for a number of covariables, such as age, gender and BMI. Differences were considered significant when $P < 0.05$. All graphs were drawn with Prism, version 5.0f (GraphPad). All statistical analyses used the SPSS 11.0 package.

Results

From a total of 1034 patients included in the French acromegaly registry, 999 patients had exploitable data and were included in this analysis. Longitudinal evaluation (at least two visits) was available for 980 patients. Data on 787 patients were updated until 2012. A total of 5611 visits (average 5.6 visits per patient) were recorded in the database, with 14047 hormonal and biochemical tests (average 14 per patient) and 2418 medical treatment prescriptions or adjustments (average 2.4 per patient). The rate of loss to follow-up was 16.5%, and 4% of patients died during the follow-up. Medical follow-up spanned a total of 6728 patient-years.

Acromegaly characteristics

Men accounted for 46% of the registry population ($n=460$). Median age at diagnosis was lower among men (43 years, interquartiles 34–53) than that among women (48.5 years, 37–58; $P < 0.0001$ vs males, [Supplementary Fig. 2A](#)). Similarly, median age at symptom onset was lower among men (37 vs 42 years, $P < 0.0001$), as were age at the last visit (50 vs 57 years, $P < 0.0001$) and age at death (65 vs 73.5 years, $P = 0.04$). Age at diagnosis did not markedly change over time ([Supplementary Fig. 2B](#)). At inclusion,

among the 934 patients for whom the information was available, 410 patients reported headache, 151 had visual defects and nine had a pituitary apoplexy. The majority of patients had a macroadenoma ($n=672$, 71% of males and 64% of females, $P=0.055$, the chi-square test). Further data on disease characteristics are available in the [Supplementary Results](#).

Disease control

Median follow-up was seven years (range, 0.6–34). At the last visit, 369 patients had inactive disease and 309 had controlled disease on medical treatment. GH and IGF-I concentrations fell markedly between baseline and the last visit ([Supplementary Results](#) and [Supplementary Figs 3, 4](#)). The proportion of patients with controlled

Figure 1

Evolution of disease status across 4-year follow-up periods in the French acromegaly registry. Histograms indicate the percentages of patients (s.d.). Details of disease status are reported in the main text.

Figure 2

Trends in disease control. Data are the percentages of patients at inclusion and at the last visit. Disease control was defined with various IGF-I cutoffs, expressed as normalized values above the upper limit of normal (ULN) according to sex and gender (see main text).

acromegaly increased over time, whereas the proportion of patients with uncontrolled disease fell (Fig. 1 and Supplementary Fig. 5). The proportion of patients with inactive disease (i.e., patients cured after surgery and/or radiotherapy, with no ongoing medical treatment) did not change markedly. When disease control was analyzed in 4-year follow-up periods, the proportion of patients with uncontrolled acromegaly fell from 54% before 2001 to about 25% after 2010, whereas the proportion of patients with medically controlled disease rose from 18% to 42%. The proportion of patients with inactive (cured) disease was relatively stable, at between 25% and 35% (Fig. 1). These temporal trends persisted after controlling follow-up duration in the register (data not shown). Among the 265 patients with uncontrolled disease at the last visit, 51% had IGF-I levels below $1.5 \times \text{ULN}$. The proportion of patients with IGF-I levels above $4 \times \text{ULN}$ fell from 19% at inclusion to 5% at the last visit (Fig. 2). Further data on biochemical control are available in the Supplementary Results and Figures.

Treatment

A multimodal therapeutic strategy was necessary in 570 patients, as illustrated in Fig. 3A.

Surgery was performed in 784 patients (79.6%). Thirty-four and 4 patients required second and third surgical interventions respectively. The proportion of patients who underwent surgery did not change

Figure 3

Treatment strategies used in the French acromegaly registry. Data are numbers of patients. Open bars indicate patients with controlled disease (≤ 1 IGF-I ULN). Closed bars indicate patients with active disease (> 1 IGF-I ULN). (A) Treatment modalities. MT, medical treatment; RT, radiotherapy. (B) Medical treatments: somatostatin analogs (SSA), dopamine agonists (DA) and combinations. The numbers of patients with controlled/uncontrolled disease are shown in the Panel B inset, according to single-agent or combination therapy.

significantly over time (Fig. 4A). When considering patients for whom postoperative biochemical data were available at least 3 months after surgery, IGF-I levels were normal in 48% of cases. The proportion of patients with normal postoperative IGF-I levels was higher among those with a microadenoma (60.2%) than among those with a macroadenoma (41.5%, $P=0.0016$).

Radiotherapy (conventional fractionated or stereotactic radiosurgery) was performed in 188 patients, as an adjuvant to surgery and/or medical treatment in 77% of cases. The proportion of patients who underwent radiotherapy fell gradually over time (Fig. 4A).

Medical therapy was prescribed in 710 patients. The drugs used, and their combinations, are shown in Fig. 3B. The proportion of patients with uncontrolled vs controlled disease did not differ according to the choice of drug or the use of single-agent vs combination therapy (Fig. 3B and insert). The use of pegvisomant increased

Figure 4

Evolution of treatment strategies. Data are the percentages of patients. (A) Distribution of treatment approaches in different follow-up periods. MT, medical treatment; RT, radiotherapy. (B) Evolution of drug therapy in medically treated patients: somatostatin analogs (SSA), dopamine agonists (DA), GH receptor antagonist (GHRA). The histograms report the prescribed classes of treatment per patient according to different follow-up periods, and thus, repeatedly include patients receiving more than one treatment.

Note: pegvisomant was approved for the treatment of acromegaly in France in late 2003.

over time, whereas that of somatostatin analogs (SSA) declined (Fig. 4B).

Partly caused by local therapeutic possibilities, drugs were the first-line treatments for 49.6% of patients overall, rising from 30% before 2001 to 45% in 2001–2006 and 54% in 2007–2012. However, it must be underlined that 63% of patients receiving first-line medical treatment underwent a subsequent neurosurgical intervention. The use of first-line medical treatment was influenced by age ($P<0.0001$), BMI ($P<0.0001$), T2DM ($P=0.004$) and cardiac ($P<0.0001$), respiratory ($P<0.0001$) and cerebrovascular ($P<0.0001$) comorbidities. The use of first-line medical treatment was not associated with microadenoma versus macroadenoma status at diagnosis, or with tumor size, but it was associated with laterosellar extension of a somatotrope tumor ($P<0.0001$).

Cardiovascular comorbidities

Information on cardiac comorbidities was available for 943 patients at inclusion. Hypertension was recorded in 33% of cases, heart valve disease in 10.8%, heart failure in 1.9%, coronary artery disease in 1.6%, myocardial infarction in 0.7% and arrhythmias in 3%. In a subgroup of 85 patients with available echocardiographic findings, 36 patients were found to have myocardial hypertrophy. Systolic (but not diastolic) blood pressure fell significantly between baseline and the last visit (Supplementary Fig. 6G and H). At the last visit, only 43 patients had developed incident heart disease (mainly arrhythmias, valve disease and hypertension). Incident heart failure occurred in 2 patients and ischemic heart disease in 3 patients (Supplementary Table 1). In a logistic regression model, ULN IGF-I levels at baseline were associated with myocardial hypertrophy and valvulopathy ($P=0.004$ and 0.016 respectively), but not with cardiac comorbidities as a whole. These associations disappeared after adjustment for age. Similarly, GH levels at baseline were associated with heart failure ($P=0.011$), but this association disappeared after adjustment for age.

Cerebrovascular events and arteriopathy were recorded in 14 and 6 patients respectively and occurred during follow-up in three cases and one case respectively (Supplementary Table 1).

Metabolic comorbidities

T2DM was diagnosed in 22% of the 941 patients for whom relevant test values were available. Some metabolic parameters improved during follow-up (Supplementary Fig. 6A, B, C, D, E and F). Mean fasting plasma glucose ($P<0.01$), glycosylated hemoglobin ($P<0.05$) and triglyceride ($P<0.001$) levels were significantly lower at the last visit than those at baseline. No significant difference was found in the levels of total cholesterol or its fractions (trend for LDL decline, $P=0.052$). At baseline, BMI was higher in men (median: 27.5; range: 17.4–45.2) than that in women (25.6, 17.9–43.8, $P<0.0001$). During follow-up, weight and BMI increased gradually in both men and women ($P<0.0001$ for both, Supplementary Fig. 7). A positive correlation was found between baseline ULN IGF-I levels and T2DM ($P=0.041$), even after adjustment for age ($P=0.002$), BMI ($P=0.01$) and both factors ($P=0.006$). The association between GH levels and T2DM ($P=0.024$) disappeared after adjustment for age and BMI.

Other comorbidities

Among the 926 patients for whom this information was available, 239 patients (25.8%) were recorded as having OSA, but the diagnosis was ascertained by polysomnography in only half the cases. Rheumatologic comorbidities affected 50.8% of the 923 patients for whom this information was available. A concomitant pituitary deficit was present in 30.8% of the 931 patients for whom this information was available, mainly affecting gonadotrope (22%), corticotrope (9.9%) and thyrotrope (9.1%) function. Further details on respiratory and rheumatologic comorbidities and pituitary function are available in the Supplementary Results. Few new comorbidities occurred during follow-up (Supplementary Table 1).

Cancers

One hundred and two cancers were diagnosed in 94 of the 926 patients for whom this information was available. However, 69 of these cases were diagnosed at inclusion or during follow-up. The SIR for incident cancers, compared to the general French population during the same period, was 1.34 (95% CI: 0.94–1.87) in men and 1.24 (95% CI: 0.77–1.73) in women. The organ distribution of cancer was broad, with a noteworthy incidence of breast, thyroid and colorectal malignancies (Supplementary Table 2). Neither GH nor ULN IGF-I levels were associated with the occurrence of cancer or with the tumor site. The registry mentions 175 cases of colorectal polyps, identified by 534 colonoscopies, of which 29 cases were detected during follow-up. ULN IGF-I levels correlated with the presence of polyps, even after adjustment for age, BMI and smoking, both separately and together ($P=0.001$, 0.004, 0.001 and 0.002 respectively). GH levels did not correlate with the presence of polyps.

Mortality

Forty-one patients (22 women and 19 men) died during follow-up, at a mean age of 62.8 years. The SMR was 1.05 (95% CI: 0.70–1.42). The causes of death, in decreasing order, were cancer ($n=14$), cardiovascular or cerebrovascular events ($n=9$), respiratory complications ($n=4$) and road accidents ($n=6$). The cause of death was not reported for nine patients. The incidence of death by gender as a function of age in the entire persons-year cohort is reported in Fig. 5.

Deaths

Figure 5

Mortality in the French acromegaly registry. The gray histograms represent the person-years contribution in men (upper panels) and in women (lower panels). Individual events are plotted for men (upper panels, squares) and women (lower panels, circles) in the same age groups.

Discussion

This is the first comprehensive analysis of the French cohort of patients with acromegaly. Two previous studies focused on specific issues (23, 24). The disease characteristics of this cohort are wholly concordant with those reported in other registries and large series. Nevertheless, some of our results are original or confirm recent data in the trends and management of acromegalic comorbidities. We observed noteworthy changes in the management of acromegaly over time. In particular, the proportion of patients whose disease was controlled was far higher in recent years than when the registry was created more than 3 decades ago. We also noted a gradual increase in the use of first-line medical treatment and of pegvisomant as part of multimodal treatment. We also found that acromegaly is no longer associated with excess mortality or increased cancer incidence. Furthermore, cardiovascular disorders are no longer the leading cause of death, being displaced by cancer as in the general population.

As in other registries (9, 11, 12, 13, 17, 18, 21), we found a slight female predominance and earlier diagnosis in males. Table 1 compares disease characteristics in this and other national registries. As also observed in the

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Danish population (20), we found no decline in age at diagnosis over a 20-year follow-up period (Supplementary Fig. 2), further suggesting that diagnostic awareness has not improved over time. In addition, the proportion of patients diagnosed with pituitary microadenomas did not increase over time, macroadenomas remaining predominant. Older patients generally had smaller adenomas with lower somatotrophic activity, suggesting that GH-secreting adenomas are less aggressive than those in younger patients (25).

Most participating centers based their definition of disease control on IGF-I, probably because of the use of GH receptor antagonist treatment. GH levels were available at the last visit for only two-thirds of patients. Based on IGF-I levels alone, disease control was achieved in more than 70% of patients at the last visit, which is close to the proportion reported in other registries (Table 1). The rate of disease control based on mean GH <1 ng/mL or a GH nadir <0.4 ng/mL after OGTT suppression was about 50% in our registry (Supplementary Fig. 4). Whatever the criterion used, the rate of disease control rose gradually over time (Fig. 1 and Supplementary Fig. 5). This could be related to the advent of new drugs and treatment schedules or to gradual adoption of guidelines recommending more stringent criteria for acromegaly control since 2000 (4, 5, 26, 27, 28, 29). One caveat is that each participating center used its own IGF-I assay and normative data. Current recommendations for GH and IGF-I measurement (30), and the establishment of normative data for various IGF-I assays in a very large population of healthy French participants (31), should attenuate this limitation in future.

Based on IGF-I levels, about 25% of patients still had uncontrolled disease at their last visit. Nevertheless, biological disease activity in these individuals was generally mild, as IGF-I levels did not exceed $1.5 \times \text{ULN}$ in more than half the cases. Moreover, the majority of these patients had a recent diagnosis (≤ 1 year), meaning that treatment might not yet have been optimized or that drug titration was ongoing. Analysis of the German registry showed that numerous visits were often needed to choose and titrate the most appropriate drugs and thus to achieve biochemical disease control (32). Other authors have suggested that $1.2\text{--}1.3 \times \text{ULN}$ is an acceptable IGF-I target (21, 33). On this basis, almost 80% of our patients could be considered adequately controlled at the last visit. Drug resistance, suggested by elevated GH or IGF-I levels despite chronic treatment at stable doses, seems to account for only a minority of treatment failures.

The treatment strategy was multimodal in almost 60% of cases: most patients underwent surgery and received adjuvant medical treatment. As in other registries, almost 80% of our patients underwent at least one neurosurgery (Table 1). This proportion did not change over time, indicating that surgery remains the preferred strategy for cure or at least for removing as much tumor as possible to enhance the efficacy of adjuvant therapy (Fig. 4). The surgical cure rate is highly variable across published series, ranging from 37% to 88% (mean 61.2%) (34). A large proportion of the 380 patients in our registry whose IGF-I level normalized after surgery had microadenomas, as in other series (34). In contrast, the proportion of patients who received radiation therapy fell gradually with time (Fig. 4A), as in other national registries and series (8, 9, 35).

The majority of our patients received medical treatment (Fig. 3). A variety of drugs were being used at the last visit, as in other registries, most patients still being treated with somatostatin analogs. The percentage of patients on SSA declined, whereas the percentage of patients on pegvisomant increased; this latter drug became available in France in 2003. Pegvisomant provides control of acromegaly in most cases resistant to conventional drugs (36, 37, 38). No data on pasireotide are available, as this drug was only recently marketed in France. Compared to most published series, a high proportion of patients included in the French Registry received first-line use of medical treatment, and this proportion increased over time (Fig. 3 and Table 1). This trend could be related to a lack of expert pituitary surgeons in some centers in France and to difficulties in referring patients to centers outside their administrative region, partly owing to cost considerations. In addition, first-line medical treatment is preferred for elderly and obese patients, as well as for patients with serious comorbidities such as diabetes or cardiac, cerebrovascular and respiratory disorders. The choice of first-line medical treatment is also influenced by tumor characteristics, as some aggressive or laterally extensive adenomas cannot be fully excised.

Data on comorbidities are less frequently available in other national registries (Table 1). Cardiovascular disease is reported to be highly prevalent: for example, hypertension is found in 11–54% of patients, depending on the series (Table 1). The prevalence of cerebrovascular disease in our cohort (4%) was similar to that in the Belgian (5.6%) and Spanish (7.1%) registries (Table 1). This is at variance with the results of specific studies (7, 39), possibly owing to the lesser use of radiotherapy in most recent cohorts (40) or to differences in cardiovascular risk factors and events

Table 1 Comparison of national acromegaly registries: disease characteristics and comorbidities.

Country	Year	Patients, n (M)	Age DG (M/F) (years)	F-up duration (years)	Macro- adenoma (%)	DC (%)	SURG (%)	MT (%)	RT (%)	MT 1st (%)	HT	CaV	CeV	T2DM	AP	CT	OSA	CLD	PD	CP	Cancer	Ref.
New Zealand	2004	208 (125)	42	12	84	61	82	0	87	0	54	-	-	30	69	-	-	-	68	-	-	7
Finland	2005	334 (161)	48	22	67	76	87	29	35	-	-	-	-	-	-	-	-	-	-	-	-	8
Belgium	2007	418 (213)	42M, 46F	11	79	56	68	78	34	23	39	18	6	25	47	28	17	-	40	27	11	9
Greece	2011	115 (45)	47	9	74	52	79	51	29	26	46	50	-	25	-	-	-	-	8	55	-	10
Italy	2012	1512 (624)	45	10	70	65	80	75	24	-	33	-	-	16	-	-	-	-	-	-	-	11
Spain*	2004	1219 (478)	-	-	-	-	-	-	-	-	39	14	7	38	20	19	13	5	26	10	8	12
	2013	1658 (646)	46	11	75	76	84	75	36	42	-	-	-	-	-	-	-	-	-	-	-	13
Canada	2013	649 (329)	45	10	79	70	89	65	22	15	37	-	-	28	-	-	33	-	23	-	9	14
USA	2013	166 (51)	50	7	-	72	80	74	20	-	-	-	-	-	-	-	-	-	-	-	-	15
UK	2013	2572 (1294)	47	11	-	59	70	60	45	39	-	-	-	-	-	-	-	-	-	-	-	16
South Korea	2013	1350 (627)	44	4	83	46	90	46	9	3.9	-	-	-	-	-	-	-	-	-	-	-	17
Germany	2013	1344 (569)	41M, 47F	9	81	72	89	43	22	-	-	-	-	-	-	-	-	-	-	-	-	18
Bulgaria	2014	534 (185)	41M, 41F	7	70	51	86	49	30	7	-	-	-	-	-	-	-	-	-	-	-	19
Denmark**	2016	405 (214)	49	11	69	-	67	41	17	-	11	-	-	12	-	-	-	3	-	-	-	20
Mexico	2016	2057 (834)	41	6	74	42	72	68	21	26	27	-	-	30	-	-	-	-	-	-	-	21
Malta	2012	47 (22)	43	15	77	-	72	70	53	-	47	14	-	40	30	26	6	-	66	15	11	22
France	Current	980 (460)	46	7	67	75	80	72	17	50	33	15	1	22	38	30	26	3	31	28	10	Current

*Disease characteristics and comorbidities have been reported in two separate publications. **Data are expressed as hazard ratios vs a control population, and not as individual values. AP, arthropathy; Ca V, cardiovascular events; CeV, cerebrovascular events; CLD, chronic lung disease; CP, colonic polyps; CT, carpal tunnel syndrome; CV, cardiovascular; DC, disease control; DG, diagnosis; HT, arterial hypertension; MT, medical treatment; MT 1st, first-line MT; OSA, obstructive sleep apnea; PD, any pituitary hormone deficiency; RT, radiotherapy; SURG, neurosurgery; T2DM, type 2 diabetes mellitus.

in the reference populations. It is noteworthy that three of the patients who experienced incident cerebrovascular events in our cohort had previously received conventional radiotherapy.

Diabetes mellitus and impaired glucose tolerance were present in about 22% of patients at inclusion in the French Registry. Preliminary data on glucose metabolism in 519 patients from this registry have already been published (24). Elevated IGF-I levels were associated with T2DM, independently of age and BMI. A number of metabolic parameters, such as fasting glucose, HbA1C and serum triglycerides, improved significantly during follow-up, confirming previous publications (41). Of note, mean BMI and body weight were higher at the last visit than at diagnosis, as reported elsewhere (42).

Adenomatous colorectal polyps were found in 28% of the 534 patients who underwent colonoscopy, a figure very similar to that found in the Belgian register (9), but somewhat higher than that in the Spanish register (12, 13). A previous meta-analysis showed a prevalence of colon adenomas of 23%, with a pooled odds ratio of 2.5 (95% CI, 1.9–3.2) (43). New polyps were found in only 25 of our patients (Supplementary Table 1). Acromegaly control is reported to be the best predictor of the absence of new polyps (44). In our cohort, ULN IGF-I levels predicted the presence of colorectal polyps, independently of age, BMI and gender. This confirms the well-accepted recommendation to perform periodic colonoscopy in patients with uncontrolled disease (6). Apart from colorectal polyps, ULN IGF-I no longer correlates with the presence of the other comorbidities after adjustment for potential confounding factors, particularly age. This might suggest that, in patients with acromegaly, increase in age may confer a particular susceptibility to different related comorbidities.

Ten per cent of our patients developed cancer, a figure similar to that observed in other registries (Table 1). It is noteworthy that most cancers were detected within the first 2 years after diagnosis of acromegaly, possibly during the evaluation of comorbidities focusing on the thyroid, colorectal region and breasts (44).

Forty-one deaths occurred during follow-up, a mortality rate not significantly higher than that in the French general population (SMR, 1.05; 95% CI, 0.70–1.42). When evaluating SMR, it must be acknowledged that a minority of patients included in the Registry were followed in Belgium and Switzerland. However, these countries have very similar age- and sex-adjusted mortality rates. Some other patients, lost to follow-up or with unavailable information, may also have died. Nevertheless, our

data tend to confirm that mortality among patients with acromegaly no longer exceeds that of the general population, whatever the country or continent. Indeed, a recent Mexican study showed a reduction in mortality in the acromegalic population, which was tentatively attributed to current multimodal therapy (33). Our finding that cancer was the leading cause of death, rather than cardiovascular or cerebrovascular disease (34% vs 22%), also confirms recent trends observed in other populations (11, 33). It should however be noted that, in France, in the general population, cardiac disorders accounted for 34% of deaths in 2000 but only 25% in 2013, whereas the part of cancer-related deaths rose from 23% to 29% (National Institute of Health Surveillance, <http://www.invs.sante.fr>).

The main strength of the French Registry lies in the huge amount of clinical and biological data it has accumulated, but several limitations must be underlined. The most important is that parts of data were retrospective, which may have introduced some bias. Another limitation derives from the coverage of acromegalic population by this register. Indeed, the majority of centers were tertiary referral centers and management of acromegaly proposed by these referral centers might not be fully representative of that provided to patients with acromegaly in the general population. Information on clinical features and comorbidities is mainly gleaned from the patients' standard clinical files, which may be completed differently in the participating centers. Finally, the absence of external monitor may have in part reduced the amount and quality of available information.

In conclusion, in France, at least in the centers that participated to this register, the vast majority of patients with acromegaly are now cured, controlled or at least near-normalized (IGF-I <1.5 ULN). This improvement does not seem to be related to earlier diagnosis or to a secular change in the biology of GH-secreting adenomas. Successful disease control seems to depend on several factors, such as multimodal therapy combining various medications that allow complying with the more stringent biochemical criteria recommended by the latest guidelines. These improvements in disease control, along with better management of comorbidities, probably explain why the life expectancy of patients with acromegaly is now close to that of the general population.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-16-1064>.

Declaration of interest

P C has received unrestricted research and educational grants from Ipsen, Novartis and Pfizer as Head of the Service d'Endocrinologie et des Maladies de la Reproduction, Hôpitaux Universitaires Paris-Sud, he has served as investigator (principal or coordinator) for clinical trials funded by Novartis, Pfizer, Ipsen, Italfarmaco and Antisense, he is member of Advisory Boards from Ipsen, Novartis and gave lectures for Ipsen, Novartis and Pfizer; All the fees and honoraria are paid to his institution. F B C is a member of Advisory Boards from Ipsen, Novartis and Pfizer. C C R has served as investigator (principal or coordinator) for clinical trials funded by Novartis and Ipsen, she is member of Advisory Boards from Ipsen and Novartis. All the fees and honoraria are paid to her Institution. L M, T B, A B, P P, O C, P F and J B have nothing to declare.

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