Diabetes in acromegaly, prevalence, risk factors, and evolution: data from the French Acromegaly Registry

Sandrine Fieffe, Isabelle Morange, Patrick Petrossians, Philippe Chanson, Vincent Rohmer, Christine Cortet, Françoise Borson-Chazot, Thierry Brue, Brigitte Delemer, and The French Acromegaly Registry

Service d’Endocrinologie, Hôpital Robert Debre, CHU de Reims, Rue Du General Koenig, 51092 Reims, France 1 Service d’Endocrinologie, Diabète, et Maladies Métaboliques, et Centre de Reference des Maladies Rares d’Origine Hypophysaires, Hôpital de la Timone, F-13385 Marseille, France, 2 Service d’Endocrinologie, CHU de Liége, Domaine Universitaire du Sart Tilman, 4020 Liége, Belgium, 3 Service d’Endocrinologie, CHU de Bicêtre, 94275 Le Kremlin-Bicêtre, France, 4 Service d’Endocrinologie, CHU d’Angers, 49033 Angers, France, 5 Service d’Endocrinologie, Clinique Marc Linquette, 59037 Lille, France and 6 Service d’Endocrinologie, Hôpital de l’Antiquaille, 69005 Lyon, France

(Correspondence should be addressed to B Delemer; Email: bdelemer@chu-reims.fr)

Abstract

Objectives: The French Acromegaly Registry records data of acromegalic patients’ since 1992 in French, Belgian (Liége), and Swiss (Lausanne) centers. We studied the prevalence of diabetes in this population looking for risk factors. Patients from one of the centers (Reims) were then analyzed more thoroughly.

Methods: This study has been conducted on all the patients recorded from 1999 until 2004 (519 patients). Evolution of cohorts was reassessed in 2009. Of the different variables recorded in the registry: age, sex, body mass index (BMI), duration of acromegaly, GH, IGF1 and prolactin levels, pituitary tumor size, hormonal deficiencies, presence, duration and treatment of diabetes, hypertension, and rheumatological disease were analyzed.

Results: The prevalence of diabetes in the registry was 22.3%. Diabetic patients were older and had a higher BMI. Compared with the data of the French Social Security, acromegalic patients showed a more precocious apparition of diabetes and prevalence was higher in each age group. Compared with non-diabetic acromegalic subjects, diabetic patients had a more prolonged evolution of acromegaly before diagnosis. The levels of GH and IGF1 were not significantly different between the two groups. Only hypertension was significantly more frequent in diabetic patients.

Conclusions: In our population, the prevalence of diabetes was estimated to be 22.3%. The GH and IGF1 levels did not appear as predictive factors for the presence of diabetes. On the contrary, age, BMI, and hypertension were significant risk factors as in the general population of type 2 diabetics.

European Journal of Endocrinology 164 877–884

Introduction

Acromegaly is a disease characterized by GH and insulin-like growth factor 1 (IGF1) hypersecretion due, in most cases, to a pituitary somatotropic adenoma (1). The diagnosis of acromegaly is usually delayed for years, exposing patients to slowly evolving chronic complications (2). This disease leads to increased morbidity and mortality linked in the first place to cardiovascular disease (3–5). Excess amounts of GH and IGF1 interacts with metabolic regulation, and indeed, GH hypersecretion is associated with hepatic and peripheral insulin resistance (6) this and also other mechanisms lead to the development of diabetes mellitus. Hyperinsulinism, insulin resistance, and diabetes are well-recognized cardiovascular risk factors in general population and may contribute as well to the increased cardiac morbidity and mortality of acromegalic patients (4, 5, 7, 8). Incidence of diabetes is diversely evaluated in clinical studies on acromegalic patients because of insufficient number of patients in the different cohorts (2). For several years, studies of rare diseases have been facilitated by construction of large registries in different countries (9). In this study we report data from the French Acromegaly Registry, which collects clinical data from acromegalic patients diagnosed since 1993 in participating French-speaking centers. The aim of our study was to precisely establish the prevalence of diabetes in this cohort and to search favoring factors for the presence of diabetes in such patients. Furthermore, we studied long-term evolution of diabetes after initiating the treatment of acromegaly. As the collection of the data in the registry was not exhaustive, we analyzed with more depth the data of a regional study led in one of the participating centers (Reims) in which all the consecutive patients diagnosed since 1993 have been included.
Patients and methods

Patients

The French Registry of Acromegaly has been initiated in 1999 by the French Society of Endocrinology. Data from patients diagnosed with acromegaly since 1993 in participating centers were recorded in a central database. Written informed consent was obtained from all subjects. Patient data were grouped in different 'visits'. Initial data were included in a so-called 'historical' visit, data at the time of inclusion in an 'inclusion' visit, and annual follow-up data were recorded in 'follow-up' visits. This study has been conducted on all the data recorded from January 1999 until July 31st 2004 and the evolution of the cohort has been analyzed in November 2009.

Methods

Diagnosis of acromegaly was based on the Cortina criteria (10): either nadir of GH > 1 ng/ml on oral glucose tolerance test (OGTT) or, especially for diabetic patients, mean GH > 2.5 ng/ml and IGF1 levels superior to upper limit of normal for age and sex. Diabetes mellitus was diagnosed using the WHO 1998 criteria (11). Patients aged 15 years or below were excluded from the study, as body mass index (BMI) and blood pressure vary in childhood. For each patient, we analyzed the following data recorded by the local investigator at the diagnosis of acromegaly: age and sex, BMI, estimated duration of acromegaly, mean plasmatic GH, IGF1 level (absolute level and percentage of the upper limit of normal for age and sex in each center), and prolactin levels, pituitary tumor size measured by magnetic resonance imaging (MRI), and presence of hormonal pituitary deficiencies. The following chronic complications were evaluated: presence, duration and treatment of diabetes, hypertension (HT), and rheumatological disease (arthralgia, carpal tunnel syndrome, or manifestation of arthrosis). The treatment of diabetes has been calibrated as follows: 0 for diet only, 1 for metformin, 2 for sulfonylureas, 3 for ther treatments, and 4 for insulin. Hormonal measurements were realized with commercial kit available in each center, and the normal reference range at each time point was used.

Statistical analysis

Quantitative variables cited in this study did not satisfy the normality test. These data were, therefore, expressed as mean, and median value, and first and third quartiles (Q1, percentile 25; Q3, percentile 75). For variables referred in the discussion, a density graph was plotted to allow a better approach of data distribution between the two groups. Comparisons in univariate statistics were made with the non-parametric Mann–Whitney U test. Count data were expressed as absolute value and percentage, and their comparisons in univariate statistics were made with the $\chi^2$ test. Risk factors were assessed with multivariate regression logistic test with an entry threshold of $<0.15$ and an exit threshold of $>0.05$. Significance threshold was set at $<0.05$ for all analyses. The SAS Software (Cary, NC, USA) was used for the statistical analyses; graphics were designed with the free R statistical Software (http://www.R-project.org).

Results

Study population

This study population is summarized in Tables 1 and 2. The mean age of acromegalic patients in the registry was 46.1 years, with a predominance of female (male to female sex ratio of 0.8). Mean duration of acromegaly based on the assessment of endocrinologists at diagnosis was 7.5 years. MRI revealed a pituitary macroadenoma in 80% of patients and endocrinological assessment demonstrated an associated pituitary deficiency in 26% of cases. Most frequently reported comorbidities were osteoarticular complications (58%) and hypertension (34%).

Table 1 Continuous variables assessed in the study population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Diabetics</th>
<th>Non-diabetics</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
<td>Q1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54</td>
<td>54</td>
<td>47</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.5</td>
<td>28.7</td>
<td>25.98</td>
</tr>
<tr>
<td>*Acromegaly (years)</td>
<td>9.47</td>
<td>10</td>
<td>4.25</td>
</tr>
<tr>
<td>Mean GH (ng/ml)</td>
<td>24.6</td>
<td>11.45</td>
<td>11.3</td>
</tr>
<tr>
<td>IGF1 (%)</td>
<td>324</td>
<td>286.3</td>
<td>202</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>51.8</td>
<td>10.8</td>
<td>6</td>
</tr>
</tbody>
</table>

*Duration of acromegaly before diagnosis.
Prevalence of diabetes and characteristics of diabetic patients

The prevalence of diabetes in the first 519 patients reported in the registry was 22.3%. When patients treated by oral antidiabetics and/or insulin were only taken into account (excluding patients under diet), the prevalence was 13%. Male to female sex ratio in diabetic patients (0.8) was not significantly different compared with non-diabetic patients (0.84, \( P = 0.85 \)). Age and BMI (Fig. 1) were significantly different in diabetic patients who were older (\( P < 0.001 \)) and had a higher BMI (\( P \leq 0.001 \)). However, there were precocious cases of diabetes with the earliest one occurring at 26 years of age.

In patients from the registry, there was a steady increase in percentage of diabetes with age (Fig. 2). Compared with the data of the French Social Security (prevalence of treated diabetes [12]) or the INSTANT study (prevalence of type 2 diabetes in the French population [13]), acromegalic patients showed a more precocious apparition of diabetes and percentages were higher in each age group. Regarding acromegaly parameters, the only significant difference observed in diabetic patients versus non-diabetic patients was a more prolonged evolution of acromegaly before diagnosis (\( P < 0.001 \)). Hormonal levels of neither GH (\( P = 0.18 \)) nor IGF1 (\( P = 0.4 \)) were significantly different between the two groups (Fig. 3). Diabetes was diagnosed at the same time as acromegaly in 46.8% of patients. For all other patients, the discovery of diabetes predated the diagnosis of acromegaly with a mean duration of 5.8 years and a median duration of 4 years. Although based on the clinical estimation and patient anamnesis, diabetes was present before the presumed beginning of acromegaly in only 9.8% of patients. Diabetes was treated with only diet in 39.8% of patients, metformin was used alone in 13% of patients, sulfonylureas or sulfonylureas associated with metformin in 29.6% of patients, and insulin in 17.6% of patients. Hypertension (HT; Fig. 4) was significantly more frequent in diabetic patients (61.5 vs 26.3%, \( P < 0.001 \)). This was not the case for rheumatological complications (\( P = 0.14 \)) or pituitary deficiencies (\( P = 0.271 \)).

### Table 2 Count variables of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Diabetics</th>
<th>Non diabetics</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>48</td>
<td>187</td>
<td>235</td>
</tr>
<tr>
<td>Females</td>
<td>61</td>
<td>223</td>
<td>284</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67</td>
<td>108</td>
<td>175</td>
</tr>
<tr>
<td>Rheumatological</td>
<td>68</td>
<td>221</td>
<td>289</td>
</tr>
<tr>
<td>Pit deficiencies</td>
<td>34</td>
<td>104</td>
<td>138</td>
</tr>
<tr>
<td>Adenoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micro</td>
<td>15</td>
<td>64</td>
<td>79</td>
</tr>
<tr>
<td>Macro</td>
<td>85</td>
<td>332</td>
<td>417</td>
</tr>
</tbody>
</table>

Diabetes risk factors in acromegaly

We performed both univariate and multivariate analyses of recorded variables. Age at diagnosis, BMI, hypertension, and duration of evolution of acromegaly were significant risk factors for diabetes in acromegalic patients on univariate analysis. Age, BMI, and HT were independent risk factors upon multivariate analysis. Presence of hypertension increased the risk of diabetes by 2.5%. For an acromegalic patient, the risk for the presence of diabetes was increased by 4.4% by age (odds ratio (OR) = 1.044) and 12.9% by additional BMI (kg/m²).

Regional study in Reims

In this center, all the consecutive acromegalic patients from 1993 until July 2004 were included. There were 74 patients of which 24 were diabetic (32%), significantly more than those in the registry (\( P = 0.04 \)).
the patients were also older (mean age, 50.2 years, in Reims versus 46.1 years, in the registry) and with a longer duration of acromegaly (mean duration, 10.6 vs 7.5 years). In this population, the same risk factors for diabetes were found (age, BMI, hypertension, and duration of acromegaly). Furthermore, we had the opportunity to study the presence of familial history of diabetes, which is an additional risk factor for diabetes not available in the registry data. We found a significant increase in this parameter in diabetic acromegalic patients ($P = 0.05$).

**Follow-up data**

Follow-up of the 114 diabetic patients after treatment of acromegaly was studied in November 2009.

Information was available in 108 cases after a mean evolution time of 5.40 years (1–12 years). Acromegaly was controlled in 67 patients (62%), of which 26 were still under medical treatment. In these patients, diabetes had disappeared in 23 (30%) cases. When acromegaly was still active, diabetes was normalized in nine out of 41 patients (22%). However, this trend did not appear to be statistically significant ($P = 0.25$). The treatment score of patients with active acromegaly was higher, but not significant, when compared with patients who were cured or controlled (mean 1.561 vs 1.299; $P = 0.12$). In the cohort of still diabetic patients, treatment had been modified as follows: 29 patients were on diet only versus 24 at diagnosis of acromegaly, 17 patients were on metformin versus 11, 18 patients were on sulfonylureas versus 25, and 12 patients were on insulin versus 16.

**Figure 2** Prevalence of diabetes based on the age of acromegalic patients.

**Figure 3** Density graphs comparing GH and IGF1 values of diabetic and non-diabetic patients at diagnosis.
Insulin treatment has been stopped in eight patients over 16 but had been initiated in four other patients. We looked for predictive factors of remission of diabetes. We evaluated age, GH, and IGF1 levels at diagnosis, remission of acromegaly after treatment, duration of diabetes, and treatment of diabetes. We found that remission of diabetes seemed likely if patients were younger ($P < 0.075$; Fig. 5) with a more recent diabetes ($P < 0.087$) treated by diet only ($P < 0.013$); although for the first two variables, $P$ values were higher than 0.05 significance value. However, there were some exceptions. In patients whose diabetes was cured, we found three patients with diabetes of more than 10 years’ duration, three patients who were treated by insulin, and eight patients whose acromegaly was not controlled but with a dramatic improvement in GH. We also compared the evolution of diabetes in GH and IGF1 ‘dissociated’ patients (patients with normalized GH but not IGF1 versus patients with normalized IGF1 but not GH) without finding significant results ($P = 0.31$ and $P = 0.36$ respectively). During this follow-up period, de novo diabetes was diagnosed in only one patient.

**Discussion**

This study is based on the French Registry of Acromegaly that collects information on acromegalic patients diagnosed since 1993 in French, Belgian, and Swiss tertiary centers to improve knowledge of this rare disease and its outcome in a real-life setting. We collected data about diagnosis, associated morbidities and their evolution, treatments, and their results. In this publication, we focus our interest on diabetes, which is known to be a frequent complication of acromegaly (2). Glucose metabolism was evaluated in all the patients in Registry, as OGTT was considered mandatory for inclusion, and our cohort of 519 patients seemed sufficient to evaluate such a frequent complication. At present, this study constitutes the most comprehensive study of cases recorded for the evaluation of diabetes in de novo acromegalic patients, although it is not an exhaustive collection of cases during the study period (1993–2004) as it represents only a fraction of what we could have expected according to the recently reevaluated prevalence of acromegaly by Daly et al. (14). The Belgian study describes a prevalence of 120 cases of acromegaly per million of inhabitants, which, reported to the French population, would predict a population of more or less 6000 acromegalic patients. We controlled our study by conducting a single-center study in which all the consecutive cases of acromegaly recorded between 1993 and 2004 have been included. Our local results agreed with the results of the whole cohort. Characteristics of acromegalic patients followed in the French Registry are similar to those reported in other series or registries considering mean age (46.1 years) as well as discrete female predominance (male to female sex ratio of 0.8) or mean duration of active acromegaly before diagnosis (7.5 years) (15–18). Complications are frequent and the consequences of a delayed diagnosis: 34% of our patients presented with arterial hypertension and 58% with rheumatological diseases. Tumors were macroadenomas in more than 80% of patients and pituitary deficiencies were present in 26% of the cases. The prevalence of diabetes mellitus among patients with acromegaly in the French Registry is 22.3%. The results from other studies reporting more than 100 patients are
shown in Table 3. Our study gives a higher prevalence of diabetes compared with the earlier studies, may be because of the modification of the criteria for the diagnosis of diabetes since 1998. The Spanish (19) and the Belgian registries (20) found a still higher incidence of 37.6 and 25.3% respectively. However, these two studies are very different from ours as their objective was to study all the known acromegalic patients followed in a defined territory. Some of the cases had been diagnosed a number of years ago. Furthermore, this complication was not evaluated specifically at the diagnosis and could concern older patients with a longer evolution time. To determine the impact of acromegaly in the prevalence of diabetes, we compared our results to the data obtained in 2005 in the general population by Social Security in France (treated diabetes) (12) and the results of the INSTANT study (prevalence of diagnosed diabetes in a representative sample, either treated or not) (13). Global prevalence of diabetic patients treated by oral antidiabetic drugs or insulin was 3.6% in Social Security data, 4.5% in the INSTANT study, and 13% in our cohort. When results were stratified by age and gender, acromegaly increased the incidence of diabetes particularly in younger people (30–50 years old) and in women. Diabetes was diagnosed in half of the cases at the same time as acromegaly. In only 9.6% of the cases, diabetes preceded acromegaly and only one patient developed diabetes during follow-up. Furthermore, after treatment of acromegaly, diabetes disappeared in 30% of the cases and treatment could be reduced in a number of other cases. The likelihood to control diabetes increases if acromegaly is also controlled. In another study evaluating comorbidities in strictly controlled acromegalic patients, the prevalence of diabetes was not different (11%) from a large control group (8.5%). All these results confirm the large implication of GH excess for the prevalence of diabetes. However, we could identify neither GH nor IGF1 level as significant risk factors for diabetes. Variability in different commercially available kits for measuring GH and IGF1 might have confused the role of hormone concentrations in the presence of diabetes. Another way to find the impact of excessive GH is to estimate the duration of acromegaly, although it is a clinical parameter, which is very difficult to assess.

We found that diabetic patients had a significantly longer evolution of acromegaly, but disease duration did not appear as an independent variable on multivariate analysis. Although not directly related to acromegaly, we were able to demonstrate three independent parameters: age, BMI, and hypertension. In our local study, familial history of diabetes appeared as a possible additional factor. These parameters have nothing to do with acromegaly per se but are rather related to what is known about diabetes risk factors in the general population. Few other authors have addressed this question. Wass et al. (21) have analyzed the data of 69 acromegalic patients and did not find any parameter in relation with occurrence of diabetes. Nabarro et al. (17) have reported the results of a large cohort of 208 patients among which 48 had diabetes. They found a significant correlation between age, duration of evolution of acromegaly, and GH level with the presence of diabetes but only by univariate analysis because of the insufficient size of the cohort. Finally, Biering et al. (22) have identified age but not GH level as risk factor for diabetes. Møller et al. (23) have studied insulin resistance in acromegalic patients before and after adenomectomy. They have demonstrated that insulin resistance in acromegalic patients is relieved after adenomectomy. Normalization of glucose response to insulin may explain why in our patients glucose metabolism was improved and the prevalence of diabetes reduced to that of the general population.

The precise mechanism of insulin resistance in the presence of excessive chronic GH is still not clear. GH has a short-term insulin-like effect, but chronic exposure impairs insulin response. Cross talk between GH receptors and insulin receptors have been demonstrated, both sharing some post-receptor signaling pathway elements. Insulin receptor substrate-1 (IRS-1) and phosphatidylinositol 3-kinase (PI3K) appear as the two main elements of this cross talk. In vitro and in vivo studies have shown different effects, which complicate further the understanding of the mechanism. A decrease in glucose transporter has also been hypothesized as one of the mechanisms of hyperglycemia. Uncoupling between PI3K and its downstream signals, and IRS inhibition could reduce IR response. This effect predominantly appears in the liver. Secondary hyperinsulinism may also down-regulate IR (for a review of these mechanisms, see Dominici et al. (24) and Møller et al. (6)). Recently, liver IGF1 receptor-deficient mice have shown that IGF1 also plays a role in insulin sensitivity (25). Modulation of glucocorticoid metabolism through the activity of 11β-hydroxysteroid dehydrogenase may also add another level to the complexity of glucose metabolism regulation under GH and IGF1 (26).

We also looked at the evolution of diabetes in patients with ‘dissociated’ GH and IGF1 (patients that normalize only IGF1 or GH) hypothesizing a difference in glucose metabolism in these two groups. No significant
difference was found when comparing these two groups of patients. Another question that arises is the impact of different treatments of acromegaly in the evolution of diabetes. In our registry, there are different approaches in treatment (some centers treat each patient with somatostatin analogs (SSA) for at least 3 months before surgery, others not; some centers use more frequently radiotherapy, etc.) and the size of the cohort does not allow for a statistically significant stratification of patients based on different treatment schemes. Ronchi et al. (27) have compared two somatostatin analogs (octreotide LAR versus lanreotide SR) describing a decrease in insulin resistance with both drugs, octreotide LAR appearing more detrimental to diabetes than lanreotide. In a study by Colao et al. (28), where a group of patients was treated for 5 years with somatostatin analogs, no significant change was noted on the prevalence of diabetes during the study duration, although HOMA-R and HOMA-β significantly decreased. These authors have also assessed glucose tolerance (GT) in patients treated for 12 months by SS analogs (29). Disease control, GH level, and initial GT were the major predictors of the evolution of GT in this cohort. Mazziotto et al. (30) have studied the effect of high doses of SSA on glucose metabolism of patients whose acromegaly was inadequately controlled with standard doses of SSA, showing a low impact on glucose metabolism that was related with biochemical markers of acromegaly. Moller et al. (23) have showed a complete reversal of insulin resistance and glucose and lipid metabolism in acromegalic patients cured by adenomectomy. In a study by Kinoshita et al. (31), glucose metabolism in patients cured by surgery was improved when patients had preserved β-cell function. Colao et al. (32) have also tried to compare glucose metabolism in four groups of patients treated by SSA alone, surgery alone, or a combination of the two, showing an improvement in some patients under SSA, and a similar deterioration in all groups. To compare the impact of different treatments on glucose metabolism, we will probably need prospective studies with strict treatment protocols.

Conclusions
This study based on the French Acromegaly Registry, helps to further approach the prevalence of diabetes in acromegaly. In this population, the prevalence of diabetes was estimated to be 22.3%. GH and IGF1 levels did not appear as predictive factors for the presence of diabetes. On the contrary, age, BMI, and hypertension were significant risk factors. These risk factors are also found in the general population of type 2 diabetes. Thus, acromegaly could represent a strong sensitizing factor revealing a latent type 2 diabetes. Management of this complication is an intrinsic part of the management of acromegaly.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
The French Acromegaly Registry was founded with the help of an unrestricted educational grant from IPSEN, Novartis, and Pfizer. The members of the French Acromegaly Registry not in the author list are: Sonnet E, CHU de Brest, France; Cazabat L, Cochin Hospital, Paris, France; Hieronimus S, Hospital de L’Archet, Nice, France; Gaillard R, CHU de Lausanne, France; Enjalbert A, CHU la Timone, Marseille, France; Raineiraud I, CHU de Montpellier, France; Dupuy O, Hôpital d’instruction des Armées Béguin, St Mandé, France; and Beckers A, CHU de Liège, Belgium.

References