CLINICAL STUDY

GH deficiency in adults: an epidemiological approach

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Abstract

Objective: The prevalence of adult onset GH deficiency (GH-D) is poorly documented. Epidemiological data are now required to estimate the financial cost of GH treatment in adults. The aim of the present study was to estimate the prevalence of GH-D, from a cohort of 1652 adult patients with hypothalamo–pituitary diseases.

Design: The hormonal status of all patients presenting with pituitary disease and observed during the year 1994 in 15 endocrine units was retrospectively analyzed, irrespective of the date of disease onset, of the nature and date of pituitary investigations, and whether or not they included specific testing of the GH axis. Of the whole population of 1652 patients, a selected group (RG2) was chosen after exclusion of patients with active acromegaly ($n = 1414$).

Results: GH stimulation tests had been performed in 549 patients of the RG2 group and a documented GH-D was found in 301. A relationship between the value of the GH peak and the number of pituitary deficits was evaluated. For instance, it was shown that 93% of patients with three deficits had GH-D. These results constituted the basis for estimating the number of GH-D in the group of untested patients. The number of GH-D deduced from the number of established GH-D ($n = 301$) and from the number of GH-D hypothesized from other pituitary deficits ($n = 406$) was 707 cases. Prevalence and annual incidence were calculated from data recorded in a referral center with a well-defined catchment area, Marseilles (Bouches du Rhône department). We projected a prevalence of 2638 for France and an annual incidence of 12 GH-D per million of the adult population.

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Introduction

The prevalence of adult onset growth hormone (GH) deficiency (GH-D) is poorly known, since GH testing was not commonly performed until GH treatment was available in adults. In addition, the number of GH-D children cannot be automatically converted to adults with GH-D, since diagnosis was not confirmed when GH status was re-examined in adulthood in a number of patients previously treated for childhood idiopathic isolated GH-D (1–3).

The description of the clinical features of GH-D in adults (reviewed in 4) and the demonstration of beneficial effects of GH replacement therapy (reviewed in 5) have prompted more extensive GH testing in adults. Although some difficulties are encountered in making a diagnosis, especially in older, sedentary

patients (6–9), a threshold of GH response to provocative tests has emerged from clinical studies carried out in the adult population (reviewed in 10).

It is now advisable to estimate the financial cost of GH treatment in adults, on a nation-wide scale. It has been reported that in adult patients the presence of multiple pituitary deficits (PIT-D) is associated with the most severe forms of GH-D (11). Thus, GH status might be inferred from conventional pituitary exploration, although the occurrence of isolated organic GH-D cannot be ruled out. The aim of the present multicenter retrospective study was to estimate, from a cohort of 1652 adult patients with hypothalamo–pituitary disease, the number of GH deficit(s) based on GH exploration and on the probability of GH-D in relation to other PIT-D. Thus, the prevalence of GH-D in France was deduced by extrapolating from these data.

Subjects and methods

Study design

Since most French patients with hypothalamo–pituitary diseases are referred to teaching hospitals, we decided to retrospectively evaluate the hormonal status of all the patients presenting with pituitary disorders during the year 1994 in 15 endocrine units considered as referral centers. Patients were considered whatever the date and nature of initial disease, the nature and date of pituitary investigation, including or not specific testing of the GH axis.

This retrospective study was conducted in 1995, from files of newly and formerly diagnosed patients who had presented with pituitary disorders during the course of 1994. Patients with idiopathic hyperprolactinemia and microprolactinoma were excluded. The files of all patients presenting with pituitary disorders were reviewed by an endocrinologist who recorded individual data on pre-designed forms. These included demographic data, medical history, diagnosis and treatment of pituitary disease, estimation of pituitary function expressed qualitatively as excessive, normal or reduced, and type of substitution therapy. When available, the results of GH exploration were fully recorded (i.e. number and type of provocative tests, GH peak values). Insulin-like growth factor-I (IGF-I) levels were expressed qualitatively as excessive, normal or reduced, in order to obviate methodological differences between institutions. Pituitary investigations were considered irrespective of the date of diagnosis and of hormonal investigation.

Populations

The whole population of patients presenting with pituitary disorders in the 15 centers during 1994 comprised 1652 patients. There was a wide variability between centers in the number of recorded patients (range: 16 to 245). Characteristics of this population are given in Table 1. The year of diagnosis for pituitary disease was 1994 in 20% of patients, less than 10 years ago in 50% of patients and more than 10 years ago in 30% of patients. Classification of pituitary adenomas was based mainly on immunocytochemical data. The proportion of non-functioning pituitary adenomas (NFPA) (i.e. follicle-stimulating hormone, luteinizing hormone and/or alpha-subunit immunopositive tumors and immunonegative tumors) was 39%.

Two groups of patients were successively excluded to constitute the selected groups. Patients with GH-secreting adenomas were first excluded and therefore made up the first restricted group (RG1) of 1227 patients. Then, 238 patients with so called 'active acromegaly' were excluded, based on the following criteria: GH-secreting adenoma and elevated IGF-I or somatostatin analog treatment. Most of our results deal

Table 1 Characteristics of patients in the whole population.

Number of patients	1652
Age (years $\pm$ s.d.)	46 $\pm$ 16
< 20 (%)	4
20–40 (%)	35
40–60 (%)	38
> 60 (%)	23
Sex (%)	58 F/42 M
Pituitary tumors (%)	78
Secreting adenomas (%)	61
Non-secreting adenomas (%)	39
Other tumors (%)	14
Non-tumor pathology (%)	8
Surgery (%)	59
Radiotherapy (%)	2
Surgery + radiotherapy (%)	18
Medical treatment (%)	21

with this second restricted group (RG2) of 1414 patients.

GH exploration

Out of RG2, 549 patients underwent specific GH exploration. Sixty percent of these explorations were performed in 1994. GH assays were performed in each institutional laboratory, and were mainly polyclonal antibody assays until 1990. For instance, in 1991 IRMA were used in 90% and RIA in 10% of laboratories. A national mandatory quality control of GH assays has shown an interlaboratory coefficient of variation of 15% for GH concentration averaging 3 μ g/l (Annales du Contrôle National de Qualité, Agence du Médicament 1994, 183–190).

Different provocative GH tests were performed. An insulin tolerance test (ITT) was the most commonly performed, either as the first test, or as the second test, in 412 out of 549 patients (75%). Other tests commonly used were GH-releasing hormone in 156 patients and glucagon propranolol in 106. Fifteen patients received ornithine and two L-dopa as the second test. Sixty percent of patients had two GH provocative tests.

The diagnosis of complete GH-D was established when the GH peak during one or both provocative tests was below 3 μ g/l. A diagnosis of partial GH-D was made when the GH peak was between 3 and 5 μ g/l and a normal response when over 5 μ g/l.

IGF-I was measured in each center. The most commonly used reagents were Nichols (San Juan Capistrano, CA, USA) with extraction (60% of French laboratories) and Sorin (France) in 20%. Quality control showed a large interlaboratory coefficient of variation of 40%. Thus, only qualitative information was recorded and was available in 1041 patients from the whole population and in 805 out of the 1414 patients in RG2.

Table 2 Relationships between GH peak value and the number of PIT-D in the subgroup of patients submitted to GH explorations.

Number of PIT-D	Peak GH <3 µg/l	Peak GH 3–5 µg/l	Peak GH > 5 µg/l
0 (n = 190)	39 (20%)	21 (11%)	130 (69%)
1 (n = 125)	58 (46%)	16 (13%)	51 (41%)
2 (n = 62)	44 (70%)	7 (11%)	11 (19%)
3 (n = 172)	160 (93%)	8 (5%)	4 (2%)
Total (n = 549)	301	52	196

Data analysis

The probability of GH-D occurrence in relation to other PIT-D was calculated from the results obtained in the 549 patients who underwent both GH provocative tests and evaluation of pituitary functions. From these data, the number of GH-D in the RG2 patients who did not undergo GH exploration was estimated according to the number of their PIT-D. We postulated that the number of GH-D was the sum of cases documented by GH exploration and of estimated cases in patients untested for GH-D.

Since all institutions in the country did not participate in the study, the results were not exhaustive. A center with a monopolistic recruitment (Marseilles) was used as a reference to balance the above results and to estimate the incidence of GH-D patients in France, based on the new cases recorded in Marseilles in 1994.

Results

Results of GH exploration in RG2

Complete GH-D was found in 301/549 patients (i.e. in 55% of tested patients), partial in 52 patients (9%) and was excluded in 196 patients (36%). Only complete GH-D qualified as GH-D. The number of PIT-D associated with the results of GH exploration is shown in Table 2. These associations indicate that out of 301 patients with complete GH-D, 160 (53%) had three PIT-D, 44 (15%) had two, 58 (19%) had one and 39 (13%) had none. Conversely, when considering patients according to their PIT-D, 93% of patients with three

deficits were GH-D, and 20% of patients with no deficit were GH-D. These results were used to estimate the number of GH-D in RG2 patients untested for GH-D, according to the number of their PIT-D as shown in Table 3. Thus, the total number of GH-D estimated as the sum of the diagnosed cases (i.e. 301 patients) and of estimate cases (i.e. 406 patients) was 707 in the cohort of 1414 patients.

Estimated prevalence of GH-D in France

From this cohort, an exhaustive estimation could not be achieved because the centers participating in the study were not the only endocrine units for a given region or even for a city, and because all French regions did not participate. For these reasons, it was obvious that the reference population was difficult to define.

Thus another calculation was performed, based on the results obtained in one center with a quasi-monopolistic situation: Marseilles. It was considered such since 97% of patients (142/147) originating from the Bouches du Rhône department were recorded in Marseilles. Moreover, the ratio of the population presenting with pituitary disorders in Marseilles in relation to the population in the Bouches du Rhône department was the highest among all 15 centers. Thus, we considered that it might be more appropriate to estimate the prevalence of GH-D from the results in Marseilles than from the general results.

With the same procedures of calculation, the number of GH-D patients was evaluated as the sum of observed deficits (i.e. 27 patients), plus those estimated from other pituitary disorders (i.e. 55 patients). The total

Table 3 Extrapolation of the number of GH-D, calculated in relation to the number of PIT-D. Example: 93% of 208 patients belonging to RG2, untested for GH, and having three PIT-D, are estimated to be GH-D: $n = 193$.

Number of PIT-D	Number of patients in RG2 population	Percentage GH-D in tested subgroup (A)	Number of untested patients in RG2 (B)	Extrapolations of GH-D to untested subgroup (A×B)
0	601	20%	411	82
1	295	46%	170	78
2	138	70%	76	53
3	380	93%	208	193
Total	1414	301/549	865	406/865

Table 4 Relationships between IGF-I and the value of the GH peak, in a subgroup of patients of the RG2 group.

IGF-I	Peak GH < 3 µg/l	Peak GH 3–5 µg/l	Peak GH > 5 µg/l
Normal	74 (42%)	25 (70%)	97 (90%)
Low	100 (58%)	11 (30%)	13 (10%)

amounted to 82 patients. This result was related to the population in Bouches du Rhône (i.e. 1 759 400 inhabitants). Based on these results, the prevalence of GH-D was estimated to be 46 per million of the population. Since the French population is 56 615 000, extrapolating from these data to the whole country, we found that 2638 persons might be affected with complete GH-D in France.

Annual incidence was also deduced from the number of new patients in 1994 in Marseilles. Sixteen of these patients were found to be GH-D, for a population of 1 759 400 inhabitants, corresponding to an annual incidence close to 9 per million of the population. If only the adult population representing 75% of the whole population in the Bouches du Rhône department was considered, the incidence would reach approximately 12 per million of the adult population.

Relationship between IGF-I and GH status

In the selected RG2 population, qualitative evaluation of IGF-I according to age and sex, available in 805 patients, was normal in 71% and low in 29%. When three associated PIT-D were present, IGF-I was low in 53%. In patients with isolated GH-D (i.e. in 21 patients), IGF-I was low in 33%. The relationship between IGF-I and the value of the GH peak was studied in a subset of patients tested for GH and is shown in Table 4.

Comparison of the number of GH-D between the two selected RG1 and RG2 populations

Since 301 patients belonging to RG2 and 282 patients belonging to RG1 were GH-D, it appeared that 19 patients with previous acromegaly were GH-D.

Discussion

The present retrospective multicenter study was undertaken to estimate the number of patients with GH-D in our country, from reference centers located in teaching hospitals in close relationship with neurosurgical institutions. This study was conducted on patients presenting during one year, i.e. 1994, whatever the duration of their disease. Specific explorations of the GH axis were performed according to the practices of each institution at each period. Nevertheless, quality controls of GH assays in our country demonstrate an acceptable

interlaboratory coefficient of variation; moreover, 75% of patients were explored by ITT and 60% of patients underwent two provocative tests. Thus, even if our data do not reach the level of solidity required today for diagnosing GH-D, it can be said that more than 50% of the patients undergoing GH testing had a severe GH-D.

Since explorations of the GH axis were not systematically performed, our evaluation was partially based on a calculated probability of GH-D in patients related to the presence of other PIT-D. Our results are in agreement with previous studies showing a very high proportion of GH-D in patients with multiple PIT-D (11). These data provide a rationale for preferential exploration of GH secretion in these patients, when a therapy-making decision is at stake. However, our study suggests that the probability of a complete GH-D in patients with no other PIT-D is rather high (i.e. 20%) and cannot be neglected. Thus, if the detection of GH-D by specific exploration is targeted on the number of PIT-D, the performance of these explorations may average 93% for the patients with three PIT-D, but only 53% of patients with GH-D will be diagnosed. Thus, this selection based on associated PIT-D has excellent value in predicting positive results (i.e. complete GH-D), but its sensitivity is rather low. If patients are selected on the basis of at least one associated PIT-D, the performance of these explorations is lower, averaging 72%, but only 13% of GH-D will be lost.

IGF-I is reported to be of little value for the diagnosis of GH-D in adults (12, 13). This is in accord with our results showing that 42% of patients with GH-D have IGF-I values normal for age and sex. This is particularly true in patients with three PIT-D since only 53% of IGF-I values were low, although the probability of having GH-D was 93%. Therefore the number of PIT-D appears to be a stronger predictor of GH-D than IGF-I level.

The number of 707 patients considered to be suffering from GH-D out of a population of 1414 seems very high. This population of pituitary patients was selected by the initial exclusion of patients with microprolactinomas and the secondary exclusion of patients with acromegaly. In addition, this population followed up in teaching hospitals was formed mainly of patients at risk for PIT-D in relation to surgery and associated radiotherapy. This is reflected by the high proportion of patients with tumoral pathology and by the number of associated PIT-D. The average of 8% of non-tumorous pituitary disorders is similar to that

reported in the UK (14, 15), although in Sweden idiopathic hypopituitarism was more commonly found (i.e. 16%) by Rosén & Bengtsson (16). Thirty-nine percent of pituitary tumors were NFPA; this relative proportion parallels other reports showing averages from 25 to 35% (17, 18). This is of major interest since these tumors are the main cause of PIT-D. Taken together, our results are in accord with previous reports suggesting that pituitary and parapituitary tumors and the consequences of their treatment accounted for 70–80% of cases of hypopituitarism (14–16). The data originated in the current practices in the treatment of pituitary tumors over the past two or three decades. Changes in therapeutic options and advances in surgical and radiotherapeutic techniques will probably change the ratio of deficits.

The methodology used in the present retrospective study is not fully satisfactory. It was adopted as a compromise between a limited study in one center having a well-known reference population, and a nation-based study having the advantage of a large population with limited exhaustivity. The centers were chosen for their reputation, by implicit co-optation. However, variability in intercenter recruitment suggests that most of them did not have a monopolistic position in their region, due to our liberal system of healthcare. In the main cities and regions, only one or two institutions participated in the study and recruited only a fraction of the whole population of pituitary patients. These data had the merit of showing the frequency of GH-D in hospital populations; however, the reference population was difficult to establish. This is the reason why we decided to resort to a limited calculation based on the data from Marseilles, a city with a well-defined catchment area.

We found an incidence of 9 per million inhabitants, that is 12 per million of the adult population and a prevalence of 46 per million. Our results show a large discrepancy between incidence and prevalence of GH-D. A similar incidence of 10 per million of the population is quoted by Carroll *et al.* (5) from an estimation based on the incidence of hypopituitarism (14, 16). To our knowledge, prevalence of GH-D in adults has never been published. In a survey carried out over 38 years in Göteborg, Rosén & Bengtsson (19) reported (in abstract form) an 11.9 cases per million per year incidence and a prevalence of 300 cases per million of adult hypopituitarism. Obviously both studies differ in methodology; indeed the prevalence reported by Rosén & Bengtsson is actual, while ours is estimated. This suggests an underestimation of the prevalence in our study. The main cause may be related to the 1 year duration of the collection of cases. Undoubtedly, an unknown proportion of patients do not present every year. This is probably more common in older patients for whom follow-up may be less frequent. This is reflected by the fact that only 30% of patients presenting with pituitary disorders in 1994 were diagnosed more than

10 years before. In addition, the present study does not allow for an accurate determination of the number of patients with childhood onset pituitary disease. It may be suggested that mainly patients with organic pituitary lesions are referred to hospital endocrinologists by pediatricians. Therefore this cause of underestimation cannot be ruled out. Nevertheless, the prevalence estimated in our study reflects the number of patients who may benefit from GH treatment prescribed in teaching hospitals.

In conclusion, we confirm the major (but not exclusive) ability of associated PIT-D to predict GH-D. Pituitary status remains a valuable criterion for implementation of GH axis exploration. However, we have to bear in mind that this selection will leave out 13% of patients with GH-D.

Even if the methodology used in this study was imperfect, the results, i.e. an annual incidence of 12 per million of the adult population obtained by indirect estimation, may be of value in predicting the financial cost of GH treatment.

Nowadays, direct assessment of the GH axis is more commonly performed using conventional methods. New tools are currently under investigation (20). The results of these explorations will certainly provide more accurate data, if an appropriate prospective methodology is implemented.

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