Diagnostic strategy for growth hormone deficiency: relevance of IGF-1 determination as a screening test


original article

Introduction. – Le déficit en hormone de croissance de l’adulte doit être diagnostiqué avant la mise en route d’un traitement par hormone de croissance recombinante humaine. Nous avons étudié l’intérêt clinique d’une approche pour diagnostiquer le déficit somatotrope, en utilisant le taux d’IGF-1 comme première étape d’un dépistage.

Méthode. – En 2000 et 2001, nous avons testé 142 patients adultes avec une pathologie hypothalamohypophysaire pour leur fonction somatotrope, par hypoglycémie insulinique, (test de référence) avec dosage concomitant de l’IGF-1, marqueur de fonction somatotrope. Les patients étaient classés en insuffisance somatotrope (pic de GH < 3 ng/ml lors de l’hypoglycémie insulinique) ou normaux.

Résultats. – Un déficit somatotrope a été diagnostiqué chez 61 sujets. En utilisant une courbe ROC, un seuil d’IGF-1 de 175 ng/ml donnait une valeur prédictive négative de 89 ± 5 %. Une stratégie diagnostique avec l’IGF-1 comme premier test, puis une hypoglycémie insulinique pour les sujets ayant des concentrations inférieures à 175 ng/ml n’identifiait pas cinq sujets insuffisants somatotropes sur 61, mais évitait 46 hypoglycémies insuliniques sur 142. Il existait ainsi une réduction du coût du diagnostic d’insuffisance somatotrope de 15 %.

Conclusion. – Nous proposons l’utilisation d’une stratégie consistant en la détermination de l’IGF-1 suivie, en cas de concentration inférieure à 175 ng/ml d’une hypoglycémie insulinique de confirmation pour le diagnostic d’insuffisance somatotrope de l’adulte.

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Abstract

Background. – Adult growth hormone (GH) deficiency must be diagnosed before prescribing therapeutic recombinant human GH. We studied the clinical relevance of a diagnostic strategy for growth hormone deficiency (GHD) using IGF-1 determination as a first step.

Methods. – In 2000 and 2001, we tested 142 adult patients with hypothalamo-pituitary disorders for somatotropic function using Insulin Tolerance Test (ITT), the reference test for the diagnosis of GHD, with concomitant Insulin-like growth factor–1 (IGF-1) determination, a marker of somatotropic function. Patients were classified as GHD (peak GH concentration < 3 ng/ml with the ITT) or normal.

Setting. – Monocenter prospective study in a tertiary referral center.

Results. – GHD was diagnosed in 61 subjects. Using a ROC curve, a threshold IGF–1 concentration of 175 ng/ml yielded a negative predictive value of 89 ± 5%. A diagnostic strategy with IGF-1 determination as the first step followed by ITT for patients with an IGF-1 concentration below 175 ng/ml missed five of the 61 GHD patients, avoided 46/142 ITT and reduced the cost of diagnosis by 15%.

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Conclusion. – We propose the use of a strategy consisting of IGF-1 determination followed, if below 175 ng/ml by confirmatory ITT to diagnose GHD in adults.

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Mots clés : IGF-1 ; GH ; Insuffisance somatotrope de l’adulte ; Stratégie diagnostique ; Courbe ROC

Keywords: IGF-1; GH; Growth hormone deficiency; Adult-onset; Diagnostic strategy; ROC curve

1. Introduction

Adult growth hormone (GH) deficiency is associated with altered body composition (increased abdominal fat mass, low lean body mass and reduced bone mineral content) and with lipoprotein and carbohydrate disorders [1,2]. There is much evidence showing the benefits of GH replacement therapy on these alterations and on quality of life [3–5]. It is thus important to diagnose GH deficiency, as it allows the prescription of an active treatment.

Insulin-like growth factor-1 (IGF-1) is the metabolic effector of GH. It is produced by the liver and is mainly controlled by GH [6]. IGF-1 determination is not recommended to establish the diagnosis of adult GH deficiency, mainly due to the overlap of IGF-1 concentrations between normal and GH-deficient subjects [7]. Dynamic tests are currently recommended for the diagnosis of GH deficiency: the insulin tolerance test (ITT) is considered as the reference test [7,8]. However, ITT is potentially harmful, particularly in patients with coronary artery disease or seizure. It is not generally well tolerated. Fatigue, headaches, sweating, tachycardia and anxiety are frequent adverse events. It requires trained units in specialized centres.

Thus, we tried to improve the simplicity and safety of the diagnosis of GH deficiency. The use of diagnostic strategy with IGF-1 as the first screening step and the ITT as the second confirmatory step, has not been studied in a population admitted on routine endocrinological practise for pituitary disease. The aim of our study was to analyse the clinical relevance of such a strategy and to assess its cost-effectiveness, according to the STARD Initiative [9].

2. Subjects and methods

2.1. Patients

We prospectively studied all adult patients consecutively admitted to the Endocrinology Department of Poitiers University Hospital in 2000 or 2001.

Patients were admitted as outpatients for a hypothalamic or pituitary disorder. GH and non-GH hormone deficiencies i.e. corticotrope, thyrotropic, gonadotrope deficiencies and diabetes insipidus, were sought using standard procedures. In case of pituitary surgery, patients were tested six months at least after surgery.

Patients with a personal history of coronary heart disease or seizure, pregnant women, and patients older than 75 years were not included in the study, as ITT is not recommended in such patients for safety reasons [7]. Patients with acromegaly were not included. The ITT was carried out only when GH deficiency testing was recommended [7].

For all eligible patients, both GH and IGF-1 concentrations were determined and an ITT was performed after an ECG had been checked by a senior physician for signs of ischemic heart disease. The ITT consisted in the IV injection of 0.1 units of insulin/kg BW. Blood samples were collected 0, 15, 30, 45 and 60 min later. Blood glucose concentration was also determined to ensure that the patient was hypoglycaemic; if blood glucose concentration < 2.45 mmol/l, the ITT was not assessed.

In patients with assessable ITT, adult GH deficiency was diagnosed when GH concentration was below 3 ng/ml at all time points. Otherwise, patients were considered as non-GH-deficient.

2.2. Methods

2.2.1. Biological determinations

Blood glucose was determined using a glucose oxidase method (Roche Diagnostic – Meylan-France). GH concentration was determined using a radioimmunometric test (Irma – Kit Diasorin – Antony – France), with IS 80/505 as international standard. This kit is specific for 20 KD and 22 KD human GH. The detection limit is 0.2 ng/ml. At 1.70 ng/ml, intra and inter assay coefficients of variation are 3.9% and 2.3%, respectively. IGF-1 concentration was determined using an immunoradiometric method (Irma – Kit Nichols – Paris – France). At 310 ng/ml, inter and intra assay coefficients of variation were 1.3 and 3.3%, respectively.

2.2.2. Cost analysis

The cost of each strategy for GH deficiency diagnosis (ITT alone and cascade test including IGF-1 as a screening test) was calculated as the sum of the direct costs of the resources involved in these strategies. The direct costs consisted in one ECG (12.50 €), six GH concentration determinations (85.80 €), six blood glucose concentration determinations (31.20 €), one nurse time (17.50 €) and one physician time (38.10 €). The total cost of ITT was 185.10 €.

2.2.3. Statistical analysis

Data are presented as means ± SD, medians (interquartile range) or proportions. Quantitative variables were compared between two groups by using the Student’s test or the Mann-Whitney rank sum test, as appropriate. Differences in categorical variables were analysed using the chi-square test. Statistical
relations between the number of non-GH hormone deficiencies and GH peak value or IGF-1 concentration were assessed by ANOVA or the Kruskall Wallis test. The relationship between continuous variables was assessed using coefficients of correlation.

The ability of IGF-1 concentration to discriminate between normal and GH-deficient patients was evaluated by receiver operating characteristic (ROC) curve analysis. The cut-off for optimal clinical performance measures was determined from the ROC curve. Sensitivity, specificity and positive and negative predictive values were calculated for IGF-1 and for the cascade test strategy.

Statistical analysis was performed with SAS 8.2 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at 0.05.

3. Results

A total of 184 non-acromegalic patients were studied. There was no indication for GH testing in 22 cases, according to current recommendations [7]. Twenty patients were not assessable due to technical reasons (N = 5) or incomplete hypoglycaemia (nadir blood glucose during ITT 2.45 mmol/l, N = 15). The flow diagram of study participants is presented in Fig. 1. Of the 142 assessed patients, 61 were female and 81 were male, the mean age was 46 ± 16 years. Thirty-one patients had non tumoural hypothalamo-pituitary disorders and 111 (macroadenoma in 82, microadenoma in 10 and other tumoural diseases in 19 patients) had tumoural disease. Nadir blood glucose concentration during insulin tolerance test was 1.7 mmol/l (0.8–2.4). No serious adverse events were recorded.

3.1. Clinical and biological characteristics

GH deficiency was diagnosed in 61 subjects on the basis of the ITT. Table 1 summarizes the clinical and the biological characteristics according to the presence or absence of GH deficiency. Peak GH concentration was strongly correlated

<table>
<thead>
<tr>
<th>GH deficiency</th>
<th>No GH deficiency</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.9 ± 13.4</td>
<td>43.2 ± 17.6</td>
</tr>
<tr>
<td>Men/Women: N (%)</td>
<td>39 (64)/22 (36)</td>
<td>42 (52)/39 (48)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.7 ± 5.7</td>
<td>26.2 ± 5.4</td>
</tr>
<tr>
<td>IGF-1 (ng/ml)</td>
<td>91 (70–115)</td>
<td>176 (122–238)</td>
</tr>
<tr>
<td>Peak GH concentration during ITT a (ng/ml)</td>
<td>0.5 (0.5–1.2)</td>
<td>6.7 (5.2–12.6)</td>
</tr>
<tr>
<td>Diabetic patients: N (%)</td>
<td>8 (13.1)</td>
<td>14 (17.5)</td>
</tr>
<tr>
<td>Number of non GH pituitary hormone deficiencies: N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10 (23)</td>
<td>34 (77)</td>
</tr>
<tr>
<td>1</td>
<td>8 (24)</td>
<td>26 (76)</td>
</tr>
<tr>
<td>2</td>
<td>9 (36)</td>
<td>16 (64)</td>
</tr>
<tr>
<td>3 or 4</td>
<td>34 (87)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Tumoural pituitary disease: N (%)</td>
<td>56 (92)</td>
<td>55 (68)</td>
</tr>
<tr>
<td>Pituitary surgery: N (%)</td>
<td>49 (80)</td>
<td>29 (36)</td>
</tr>
<tr>
<td>Pituitary radiotherapy: N (%)</td>
<td>30 (49)</td>
<td>4 (5)</td>
</tr>
</tbody>
</table>

BMI: body mass index; ITT: insulin tolerance test; NS: non significatif.

a Results are effective (percentages), mean ± SD, or median (interquartile range) when specified.
with IGF-1 concentration \((r = 0.625, P < 0.0001)\) (Fig. 2). IGF-1 concentrations according to GH deficiency status are depicted on Fig. 3.

Age and BMI were negatively correlated with peak GH concentration \((r = -0.331, P < 0.0001\) and \(r = -0.283, P = 0.0013\), respectively). We also found a negative correlation between IGF-1 concentration and age \((r = -0.176, P = 0.05)\). After adjustment for IGF-1 level, age and sex were no longer associated with GH deficiency.

Peak GH concentration and IGF-1 concentration decreased significantly with the number of non GH pituitary hormone deficiencies \((P < 0.0001\) and \(P = 0.0002\), respectively). As shown in Table 1, the proportion of patients with GH deficiency was significantly higher when three or more non-GH pituitary hormone deficiencies were present \((P < 0.0001)\).

### 3.2. Diagnostic value of IGF-1-based procedures

We plotted a ROC curve of IGF-1 concentration according to the diagnosis of GH deficiency as established using ITT (Figs. 4 and 5). The area under the curve (AUC) was 85%. An IGF-1 threshold of 175 ng/ml was selected to emphasize sensitivity rather than specificity. We tested the diagnostic accuracy of several thresholds (Table 2). With a threshold of 175 ng/ml, sensitivity was 92 ± 4%, specificity was 51 ± 6% and the negative predictive value for the diagnosis of GH deficiency was 89 ± 5%. With a threshold of 125 ng/ml, which corresponds to the median IGF-1 concentration in our study population, the sensitivity was 80% and the specificity was 73%. A threshold of 84 ng/ml, as suggested in the HYPOCCS study [10], gave a positive predictive value of 92% but a negative predictive value of 67% (Table 2).

We plotted separate ROC curves of IGF-1 for patients aged above and below the median age (47 years). The AUC did not differ for these two subgroups (84% vs 81%, respectively).

Forty-one of the patients with IGF-1 concentration above the threshold of 175 ng/ml \((N = 46)\) were normal and five had GH deficiency. These five GH-deficient patients had normal IGF-1 values that did not differ significantly from those of their GH-sufficient counterparts (190 ± 83 vs 203 ± 20 ng/ml; \(P = 0.7320)\).

If IGF-1 was used as a screening test (with a concentration threshold of 175 ng/ml) and ITT as a confirmatory test, 46 out of 142 ITT would not have been performed, leading to the misdiagnosis of five GH-deficient adults. Thus, in our study population, such a procedure would misdiagnose five out of 61 GH-deficient patients (8%) and yield a sensitivity of 95% (Table 2).

The diagnostic performance of the IGF-1 threshold at 175 ng/ml was as effective in the patients with or without non GH pituitary deficiencies. The negative predictive value was 83% in those people with a non GH pituitary deficiency and 100% in those with isolated GH deficiency.

### 3.3. Cost analysis

We compared the direct costs of three different strategies.

The first strategy was systematic ITT, with no prior IGF-1 determination, followed by IGF-1 concentration determination for GHD patients, as recommended for monitoring GH treatment [5]. The cost of this strategy was 29 114.60 € for the
entire study population. The second procedure was to determine IGF-1 in all 142 cases followed by ITT for the 111 patients with an IGF-1 concentration higher than or equal to 84 ng/ml as proposed by Hartman et al. [10]. The total cost of this strategy was 28,245.50 €.

The third procedure consisted in the determination of IGF-1 for all 142 patients followed by the performance of ITT for the 96 subjects with an IGF-1 concentration below 175 ng/ml (cascade test). The total cost of this strategy was 24,358.40 €.

In our study population, our diagnostic strategy seemed to be cost-effective, reducing cost of diagnosis of GH deficiency by approximately 15%.

4. Discussion

In this 2-year prospective study, we found that IGF-1 concentration was well correlated with peak GH concentration during ITT. IGF-1 concentration was lower in patients with multiple non-GH hormone deficiencies. We confirmed that IGF-1 has a poor positive predictive value for the diagnosis of GH deficiency. However, an IGF-1 threshold at 175 ng/ml was associated with a negative predictive value leading to an effective cascade test approach. Thus, the measurement of IGF-1 concentration, followed by a confirmatory dynamic test ITT for patients with an IGF-1 concentration lower than 175 ng/l, proved to be a valid and cost-effective approach.

The population described in this study was very similar to those described in previous reports supporting that it truly represents pituitary disease patients routinely admitted in endocrinological practise, without selection bias. We found that the greater the number of pituitary hormone deficiencies, the more frequent GH deficiency as previously reported [10–13]. We found that patients without any non-GH pituitary hormone deficiency had a 20% risk of GH deficiency; this is very similar to the results of a previous French study [11]. We also observed a negative correlation between age and IGF-1 concentration, as in many reports [10,14,15].

The diagnostic procedure we propose here was developed to limit the use of ITT which can result in adverse reactions typical of symptomatic hypoglycemia, e.g. tachycardia, sweating, anxiety or headache. We chose a very feasible method with large access: IGF-1 determination. Other researchers have tried to replace ITT by other tests such as GH-RH [16,17] or hexarelin [18], but these are rather complex and potentially expensive. It has been shown, in large groups of patients with adult GH deficiency, that IGF-1 concentration (adjusted for age and sex) is low in a very high proportion of GH-deficient cases [14,15,19]. This is in good accordance with our findings: only 5 out of 61 subjects with GH deficiency had an IGF-1 concentration higher than the threshold we selected.

One study attempted to identify a specific IGF-1 concentration to establish GH deficiency [10]. Interestingly, these authors focused on the positive predictive value of IGF-1, whereas we relied on its good negative predictive value. Another study also using ROC curves produced interesting results based on IGF-1 expressed in standard deviation score. This population however is highly selected affecting the application of these results to a routine endocrinology department population. The use of SDS value rather than a crude IGF-1 level is also far less pragmatic.

The clinical relevance of our diagnostic strategy is of critical importance. This approach distinguishes individuals with GH deficiency from individuals without. This affects therapeutic options [20], as GH-deficient adults can be treated with recombinant GH, which may improve quality of life [5]. We are concerned by the imperfect diagnostic performance of the cascade test; it misdiagnosed 5/61 patients, meaning that these five patients would have been denied for recombinant GH treatment. However, the titration of recombinant GH treatment
Tableau 2
Précision des différentes approches diagnostiques testées

<table>
<thead>
<tr>
<th></th>
<th>Single test approach</th>
<th>Two-step strategy</th>
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<tbody>
<tr>
<td></td>
<td>IGF-1 (threshold 175 ng/ml)</td>
<td>IGF-1 (threshold 125 ng/ml)</td>
</tr>
<tr>
<td>True positives</td>
<td>56</td>
<td>49</td>
</tr>
<tr>
<td>True negatives</td>
<td>41</td>
<td>59</td>
</tr>
<tr>
<td>False positives</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>False negatives</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>92 ± 4</td>
<td>80 ± 5</td>
</tr>
<tr>
<td>Specificity</td>
<td>51 ± 6</td>
<td>73 ± 5</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>58 ± 5</td>
<td>69 ± 5</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>89 ± 5</td>
<td>83 ± 4</td>
</tr>
<tr>
<td>Overall accuracy</td>
<td>68 ± 4</td>
<td>76 ± 4</td>
</tr>
</tbody>
</table>

Aims to obtain normal IGF-1 concentrations, which is already the case for these patients. Furthermore, these patients could be the least likely to benefit from recombinant human GH treatment as suggested by their normal IGF-1 concentration [21] although this is disputed by others [22,23]. Interestingly, the diagnostic procedure using a very low threshold for IGF-1 [10] is not associated with a 100% positive predictive value. With this threshold, two out of 25 patients would have been misclassified as GH-deficient in our study population. We believe that our diagnostic procedure (i.e. IGF-1 threshold of 175 ng/ml) is safer than that with the low threshold (84 ng/ml) because even if some patients would not have access to GH, despite being potential candidates for this treatment, all candidates for GH treatment identified by the cascade test approach had effective GH deficiency. Conversely, with the low threshold procedure, some patients with normal GH function would receive GH therapy, which is not indicated currently.

The use of the proposed diagnostic strategy is based on the good negative predictive value of IGF-1 concentration (89%). The absence of selection criteria (except age > 75 years) in our study population and the prevalence of GH deficiency corresponding to other unselected cohorts [11] are of great importance. As negative predictive value is dependent on disease prevalence, its value increases when disease prevalence decreases and vice versa. For example, use of our cascade test approach in a population with a disease prevalence twice as low as in our study sample (as encountered in primary endocrine care) would result in a negative predictive value of 96%. Conversely, in a population with a disease prevalence twice as high (as possibly seen in patients with history of pituitary radiotherapy) the negative predictive value would remain acceptable at 76%.

Some limitations must be acknowledged. This is a monocentre study, with a fairly small number of patients. However, the study population is not selected at variance with other reports on the same topic [24] similar to those studied in other large-scale cohorts.

We had to rely on IGF-1 concentration and not on IGF-BP3 or ALS, which have been reported to be of greater diagnostic value by some [25–27], but not all authors [28]. However, the purpose of the diagnostic procedure we propose is to allow easy, routine IGF-1 determination not requiring specialized structures, as a first step. As IGF-BP3 and ALS can only be determined in highly specialized laboratories, their use may have decreased the clinical feasibility of the diagnostic procedure. A second limitation is that the IGF-1 threshold concentration (175 ng/ml) was determined using a specific method and kit. The use of other laboratory kits could result in different diagnostic thresholds. In addition, this value did not take age and sex into account. Thirdly, IGF-1 concentration could vary greatly as shown in normal volunteers [29]. Thus, the threshold of 175 ng/ml could be crossed due to this variability. However, this drawback can be overcome if IGF-1 is assessed regularly (i.e., yearly). Coupled with ITT in a diagnostic strategy such as what is proposed here, this variability will not lead to inappropriate GH therapy, but simply to a possible delay of active treatment.

In conclusion, our cascade test is a simple, feasible approach for the diagnosis of GH deficiency. It demonstrates the good negative predictive value of IGF-1 concentration for the diagnosis of GH deficiency, making it possible to minimize the use of the “gold standard” method ITT. This diagnostic procedure proved to be cost-effective. Many reports have already reported that IGF-1 concentration is lower in patients with GH deficiency than in the general population but this is the first study to propose a diagnostic procedure using IGF-1 and ITT in cascade tests. The combination of both tests would lower diagnostic costs [30], and improve patient safety. Randomised trials evaluating this type of diagnostic procedure could help to better determine its clinical relevance and cost-effectiveness. As it can be easily implemented in routine primary care, its large-scale validation is important and will require further research.

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