Abstract

Objective: The Dutch National Registry of GH Treatment in Adults was established in 1998 as an initiative of the Ministry of Health. The main goals were to gain more insight into long-term efficacy, safety, and costs of GH therapy (GHT) in adult GH-deficient (GHD) patients in The Netherlands.

Methods: Baseline patient characteristics and diagnostic test procedures were evaluated.

Results: Until January 2009 in roughly 10 years, 2891 patients (1475 men and 1416 women, mean age 43.5 ± 16.5 years) were registered. GHD was of childhood-onset (CO) in over 20% of the patients and of isolated in 11%. The most common causes of GHD were pituitary tumors and/or their treatment, craniopharyngiomas, and idiopathic GHD. In 85% of the patients, a GH stimulation test was performed, in the majority an insulin tolerance test (ITT) (49%) or a combined GHRH–arginine test (25%). In 12% of the patients, IGF1 levels were ≤ −2 s.d. combined with two or more additional pituitary hormone deficits, and in 2%, it concerned patients with CO-GHD continuing GHT in adulthood. Over the years, the test of first choice shifted from ITT toward GHRH–arginine test.

Conclusion: Nearly, 2900 patients were included in the nationwide surveillance database of the Dutch National Registry of GH Treatment in Adults until January 2009. Baseline patient characteristics are comparable to that reported previously. In 85% of these patients, the diagnosis of GHD was established by provocative testing, particularly an ITT or a combined GHRH–arginine test, with an evident increase in the percentage of GHRH–arginine tests being performed in the last years.

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Introduction

Until 1985, only small quantities of human pituitary GH were available, and therefore treatment with GH was reserved for children with GH deficiency (GHD). In 1985, four patients who were previously treated with human GH were reported to have died of Creutzfeldt–Jakob disease. Treatment with pituitary GH was banned immediately (1). Recombinant human GH became available in large amounts in 1985/1986, and as a result, GH therapy (GHT) became a treatment option to consider for more patients. In 1995, GH treatment in adults with severe GHD was approved in Europe and in 1996 in the United States (2, 3). This approval was based on studies showing that GHD in adults is associated with adverse clinical symptoms such as an abnormal body composition with increased fat mass and reduced lean body mass, reduced muscle strength and physical performance, decreased bone mineral density, an adverse lipid profile and an impaired quality of life (4, 5). Treatment with GH was reported to have beneficial effects in GHD adults (4–9). Although data on mortality were very limited at that time, a study in adults with hypopituitarism showed that life expectancy was reduced due to cardiovascular disease, and the authors suggested that this was possibly a result of GHD (10).

However, no long-term data on GHT in large patient groups were available. Furthermore, GH was no longer scarce, and there was fear of misuse of GH in non-GHD patients or even the emergence of a ‘black market’. Therefore, the Dutch National Registry of GH Treatment in Adults was established in 1998 as an initiative of the Ministry of Health.

In The Netherlands, only adults who meet the criteria for severe GHD are eligible for reimbursement of GHT. Severe GHD is defined according to the consensus guidelines of the GH Research Society for the diagnosis...
and treatment of adults with GHD, published in 1997 (11). Thereafter, these guidelines have been reviewed and updated a number of times (2, 12–15). The insulin tolerance test (ITT) is considered to be the 'gold standard' to diagnose severe GHD in adults. The combined GHRH–arginine test is a good alternative if ITT is contraindicated, although the latter may be misleading in an early stage in patients with GHD of hypothalamic origin (11, 14, 16). When two or more pituitary deficiencies are present and insulin-like growth factor 1 (IGF1) level is below the lower reference range for age and gender, GHD can be assumed, since the probability of severe GHD increases with an increasing number of pituitary hormone deficits (11, 17–19). Therefore, these patients do not require further testing (17, 18).

The most common underlying causes of GHD reported in other large surveillance databases are pituitary adenomas, both non-secreting and secreting, craniopharyngiomas, and idiopathic GHD (3, 20, 21). In about one-quarter of the patients, GHD is of childhood-onset (CO), and multiple pituitary hormone deficiencies (MPHD) are present in the majority of the patients (3, 20–22).

This is the first publication of data from the database of the Dutch National Registry of GH Treatment in Adults. The objective of this study was to analyze patient characteristics and the diagnostic procedures used in patients with severe GHD registered in The Netherlands in the period mid 1998–2008.

**Patients and methods**

**The Dutch National Registry of GH Treatment in Adults**

In 1998, the Dutch National Registry of GH Treatment in Adults was established to gain more insight into long-term efficacy, safety, and costs of GHT in GHD adults in The Netherlands. Since that time, approval of the indication for severe GHD by an independent board as well as inclusion of patient data in the registry was required for reimbursement of GH treatment from the health insurer. Treatment data of all registered patients were collected since 2002 from medical records by trained monitors. These include, among other items, data on medical history, diagnostic procedures, medical treatments, physical and laboratory investigations, bone mineral density, concomitant medication, GHT, and adverse events. All data were collected on a paper case report form and checked by the same or another monitor before entry into the national database and double checked afterward for accuracy of data entry. As an internal quality control, in about 10% of the patients, all data were collected twice by different monitors. In the period 2002–2005, for each patient, the indication for GHT was revised annually using recently collected patient data, and since 2005, this was done biennial. In addition, when GHT was started before 1998 or the first monitor visit, patient data and data on GHT were also collected retrospectively for the period prior to 1998. This national database is not financially supported by pharmaceutical companies.

The patients registered in the national database can be subdivided into three different groups, namely a treatment group, a primary control group, and a secondary control group. Patients in the treatment group are receiving GHT. Patients in the primary control group are diagnosed with severe GHD; however, for different reasons GHT is not commenced. The secondary control group comprises patients who were treated with GH in the past, but in whom treatment with GH is stopped for various reasons. Of all patients in these three categories, data were collected in order to gain more insight into the effects of GHT and the reversibility of these effects after cessation of GHT. These three groups were not defined before entering the registry and can only be defined retrospectively, since patients entered the registry with the intention to treat with GH or as patients for the primary control group (severe GHD without the intention to treat). During follow-up, some patients treated with GH stopped GHT, but they were still included in the registry, and some of these patients restarted GHT. Therefore, the number of patients actually treated with GH can be different at different time points. Furthermore, in some patients, the moment of actually starting GH was delayed, and GHT was started sometimes months or even years after patients entered the registry or patients did not start at all. Those patients can be considered primary control group patients for the period that they were GHD but not treated with GH. Thus, the composition of the three groups can only be ascertained retrospectively and can be different at different time points.

**Methods**

In order to be registered, patients had to meet the criteria for severe GHD. All patients were informed by their physician that data collection for the national registry was mandatory and linked to reimbursement of the treatment costs. A small number of patients were registered before reaching the age of 18 years, because after reaching final height, an approval of the indication for GHD by the Dutch National Registry of GH Treatment in Adults was necessary.

For the present analysis, we analyzed data not only on patient characteristics such as baseline age, sex, onset of GHD but also on the underlying causes of GHD of the patients registered till January 2009. Furthermore, diagnostic test procedures of all patients were evaluated. The treating physician of each of the patients decided which diagnostic test procedure was to be used to diagnose severe GHD. For this analysis, we divided the diagnostic procedures into three different categories.
Category 1: serum IGF1 level ≤ −2 s.d. for age and gender combined with a peak GH response below the threshold for the specific stimulation test used. Category 2: serum IGF1 concentration below −2 s.d. and two or more additional pituitary hormone deficits. Category 3: continuation of GHT in adulthood without a retest procedure in CO-GHD patients with a genetic cause for GHD or multiple pituitary deficits and evident hypothalamic–pituitary disease. In these patients, there was sufficient evidence that severe GHD was present, and therefore a retest procedure was considered not necessary.

For ITT, a peak GH response of < 3 µg/l (< 9 mU/l) was used to diagnose severe GHD (11, 14, 23). For the GHRH–arginine test, a peak GH response of < 9 µg/l (< 27 mU/l) was used as cut-off value (24). When more than one provocative test was performed, we selected one diagnostic test in the following predefined order: ITT, combined GHRH–arginine, GHRH–GH-releasing peptide-6 (GHRP-6), GHRH, GHRP-6, arginine alone, or other tests (for example arginine combined with clonidine, clonidine alone, exercise test, or t-Dopa combined with propranolol). To evaluate whether there was a trend in the type of provocative test being used over time, we divided the period in which patients were tested into 3-year categories.

### Statistical analysis

All analyses were performed using the statistical software package SPSS version 17 (SPSS, Chicago, IL, USA). Multinomial logistic regression analysis was used to analyze the change over time in the diagnostic test procedures being used. In this analysis, ITT was used as reference category. All values are presented as mean ± s.d. unless stated otherwise. A P value of < 0.05 was considered statistically significant.

### Results

Until January 2009, 2891 patients (1475 men and 1416 women) with a mean age of 43.5 ± 16.5 years entered the registry. Patient characteristics are presented in Table 1. Figure 1 shows the number of patients entering the registry per year. In the period 1999–2008, each year 220 ± 35 patients who intended to start GHT were registered (the 124 patients registered in 1998 were not included in this calculation since the registry started about halfway 1998). Over the years, a total of 45 patients who applied for GHT did not meet the diagnostic criteria for severe GHD and were therefore not included in the registry.

When, at data closure in January 2009, patients with insufficient data on follow-up (< 30 days) were excluded, the remaining group of patients totaled 2694 patients. The composition of the three subgroups (treatment group, primary and secondary control groups) in the national registry is as follows: the GH treatment group comprised of 2229 (2229/2694 = 83%) patients; the primary control group, 109 patients (4%); and the secondary control group, 356 (13%) patients. The distribution of men and women among the three treatment groups was equal. However, the patients in the primary control group were somewhat older than the patients in the GHT or the secondary control group.

As mentioned previously, the group size of these three groups was variable and depended on time-interval before the analysis was being performed.

Table 2 shows the underlying cause for GHD in all patients and for patients with isolated GHD (IGHD). In almost a third of the total group of patients, GHD was caused by a non-secreting pituitary adenoma and/or its treatment (surgery and/or radiotherapy). The second most common cause for GHD was a secreting pituitary adenoma (16.3%), ACTH-producing adenomas being most prevalent, followed by prolactinomas. In 10.9% of the patients, a craniopharyngioma was the underlying cause for GHD, and in 7.2% of the patients, GHD was idiopathic. In the patients with IGHD, radiotherapy other than for pituitary disease was the most common cause of GHD, followed by idiopathic GHD and secreting pituitary adenomas. This indicates that the etiology of GHD for the total group of patients and for patients with IGHD is different. In the total group of patients with

### Table 1 Patient characteristics.

<table>
<thead>
<tr>
<th>Category</th>
<th>n</th>
<th>mean</th>
<th>%/range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.5</td>
<td>13.9–86.5</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1475</td>
<td>51.0</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1416</td>
<td>49.0</td>
<td></td>
</tr>
<tr>
<td>Onset of GHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>626</td>
<td>21.7</td>
<td></td>
</tr>
<tr>
<td>AO</td>
<td>2265</td>
<td>78.3</td>
<td></td>
</tr>
<tr>
<td>Hormonal deficiencies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGHD</td>
<td>311</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>MPHD</td>
<td>2580</td>
<td>89.2</td>
<td></td>
</tr>
</tbody>
</table>

GHD, GH deficiency; CO, childhood-onset; AO, adult-onset; IGHD, isolated GH deficiency; MPHD, multiple pituitary hormone deficiencies.

### Figure 1

Number of patients per year entering the Dutch National Registry of GH Treatment in Adults. The Dutch National Registry of GH Treatment in Adults started mid 1998; therefore the number of patients registered in 1998 is lower.
idiopathic GHD \((n=208)\), 61.1% were males and 64.4% had CO-GHD. GHD was isolated in 27.9% of the patients with idiopathic GHD. Regarding the patients with head trauma, this group represents 1.8% of the total group of patients with GHD. Of these patients, 67.3% was male, 13.5% had CO-GHD, and 11.5% had IGHD.

In 84.7% of the patients \((n=2450)\), a GH stimulation test was performed (category 1). Mean age at the time of (re)evaluation for GHD was 43.1 ± 16.2 years. In 12.2% of the registered patients \((n=352)\), the diagnosis GHD was made on IGF1 levels \(\leq -2\) S.D. combined with two or more additional pituitary hormone deficits (category 2). In 2.4% of the patients \((n=70)\), it concerned patients with CO-GHD continuing GHT in adulthood (category 3). In a very limited percentage of patients \((0.7\%, n=19)\), we were not able to obtain data on the diagnostic test procedure used to diagnose GHD. In these patients, GH replacement was already started, sometimes years, before entering the registry. In all patients, evident hypothalamic–pituitary disease was present, and we relied on the discretion of the investigating physicians that GHT was validly started. Therefore, these patients were allowed to continue GHT.

As mentioned, in 85% of the registered patients, a provocative test was performed. Provocative testing was most frequently done by either an ITT (49%) or a combined GHRH–arginine test (25%). Sixteen percent of the patients were tested with arginine alone. 9% with GHRH alone and in 1% of the patients, another test was used. In the patients who were tested with rather unreliable GH stimulation tests, there was sufficient evidence to diagnose severe GHD based on other criteria such as a genetic cause for GHD or an IGF1 level \(\leq -2\) S.D. and two or more additional pituitary hormone deficits.

Figure 2 shows the percentage of the four most frequently used test procedures over the entry period into the registry, divided into 3-year categories. In five patients, we were not able to obtain information on which provocative test was used to diagnose severe GHD. Before 1997, an ITT was performed in the majority of the patients. Over the years, there was a significant decrease in the percentage of GHRH tests or arginine tests being performed when compared with ITT \((P<0.001\) for both analyses). On the other hand, the percentage of combined GHRH–arginine tests that were performed increased significantly over time when compared with that of ITT \((P<0.001)\), with the combined GHRH–arginine test being the test of first choice in the period 2006 till 2009. From this observation, it can be concluded that after publication of the consensus guidelines for diagnosing GHD in adults in 1997, more and more patients were diagnosed with severe GHD using the test procedures being most reliable according to the guidelines, and nowadays almost all patients with severe GHD are diagnosed after ITT or combined GHRH–arginine test.

### Table 2 Etiology of GHD for the total group of patients and for patients with IGHD.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total group</th>
<th>IGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-secreting pituitary adenoma</td>
<td>898</td>
<td>40</td>
</tr>
<tr>
<td>Secreting pituitary adenoma</td>
<td>471</td>
<td>55</td>
</tr>
<tr>
<td>ACTH</td>
<td>204</td>
<td>25</td>
</tr>
<tr>
<td>Prolactin</td>
<td>189</td>
<td>21</td>
</tr>
<tr>
<td>GH</td>
<td>72</td>
<td>9</td>
</tr>
<tr>
<td>FSH/LH</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>TSH</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>314</td>
<td>3</td>
</tr>
<tr>
<td>Idiopathic GHD</td>
<td>208</td>
<td>58</td>
</tr>
<tr>
<td>Radiotherapy other than for pituitary disease</td>
<td>185</td>
<td>82</td>
</tr>
<tr>
<td>Congenital anomalies of the pituitary region</td>
<td>184</td>
<td>28</td>
</tr>
<tr>
<td>Sheehan’s syndrome</td>
<td>130</td>
<td>1</td>
</tr>
<tr>
<td>Non-pituitary tumor in the pituitary region</td>
<td>82</td>
<td>4</td>
</tr>
<tr>
<td>Empty sella syndrome, pituitary hypoplasia</td>
<td>81</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>63</td>
<td>11</td>
</tr>
<tr>
<td>Cystic lesion pituitary region</td>
<td>54</td>
<td>1</td>
</tr>
<tr>
<td>Head trauma</td>
<td>52</td>
<td>6</td>
</tr>
<tr>
<td>Infection of pituitary gland</td>
<td>51</td>
<td>0</td>
</tr>
<tr>
<td>Birth trauma</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Genetic cause</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>Unknown</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>Meningioma</td>
<td>19</td>
<td>1</td>
</tr>
</tbody>
</table>

Three patients had a secreting pituitary adenoma that produced two different pituitary hormones. There was combined secretion of GH and prolactin in two patients, and of ACTH and prolactin in one patient.
淮able to those reported earlier (3, 20–22). The distribution of the patients and the percentage of patients containing GHD patients. Furthermore, the sex distribution of the costs of GHT by the health insurer. Thereafter, the number of patients registered each year was fairly stable.

Thereafter, the number of patients registered each year was fairly stable.

Mean baseline age was 43.5 years, quite similar to that reported in other large surveillance databases containing GHD patients. Furthermore, the sex distribution of the patients and the percentage of patients with CO- or AO-GHD and IGHD or MPHD are comparable to those reported earlier (3, 20–22). The most common causes of GHD in the total group of patients in this analysis were pituitary adenomas, craniopharyngiomas, and idiopathic GHD. This is also in accordance with earlier reports (3, 20, 21). The registry is independent of pharmaceutical companies and contains not only follow-up data of GHD adults treated with GH but also follow-up data of a primary and a secondary control group. This is in contrast to reports of post-marketing surveillance studies. Therefore, we believe that the database of the Dutch National Registry of GH Treatment in Adults is a representative and useful tool, and of additional value in the research of long-term effects and safety of GHT in adults with severe GHD.

In the majority of the registered patients (85%), GHD was diagnosed by a low serum IGF1 level combined with a peak GH response below the threshold for the specific stimulation test. In most patients, IGF1 level was below −2 s.d.; however, in some patients, IGF1 concentration was between −1 and −2 s.d. A normal IGF1 level does not rule out GHD in patients with a high probability of GHD (4, 11, 13, 18). Since all patients suffered from evident hypothalamic–pituitary disease and peak GH response to provocative testing was below the cut-off for the specific provocative test used, all patients were considered to be with severe GHD. In 12% of the registered patients, severe GHD was diagnosed based on IGF1 level below −2 s.d. and two or more additional pituitary hormone deficits. As GHD is more severe with an increasing number of pituitary deficiencies, there is a very high probability of the presence of severe GHD in these patients (19). In a very limited number of patients (2%) registered with CO-GHD, no retest procedure was performed, since there was convincing evidence of severe GHD continuing in adulthood, for instance as a result of genetic mutations or empty sella syndrome. In our opinion, there was sufficient evidence for the existence of severe GHD in all patients registered in this national database.

Overall, provocative testing by ITT or GHRH–arginine test was performed in nearly three-quarters of the patients, in 49 and 25% respectively. Recently, two similar analyses of provocative tests were used within two large international surveillance databases, namely the Pfizer International Metabolic Database (KIMS) and the Hypopituitary Control and Complications Study (HypoCCS) (3, 25). Within KIMS, there are striking regional differences in the diagnostic test procedures being used with ITT more frequently used in the European countries, in contrast to the United States. The glucagon and arginine tests are also used in a considerable number of patients. However, the GHRH–arginine test is only used in a limited number of patients (25). This is in contrast with our results, where the GHRH–arginine test is frequently used and is even the test most frequently used to date. These regional differences could be the result of differences in clinical settings, health care systems, or by limited availability of GHRH in some countries (25).

Our results show a shift in testing procedures over the years, from the ITT being the test of first choice until halfway through the first decade of this century toward the GHRH–arginine test in the last few years. In a recent study within the HypoCCS database, the percentage of the use of ITT remained constant over the period 1996–2005. In contrast, there was a significant increase in the use of the GHRH–arginine test, whereas the use of arginine, clonidine, and L-Dopa tests decreased (3). In both the HypoCCS database and the database of the Dutch National Registry of GH Treatment in Adults, the ITT and GHRH–arginine test are performed in the majority of patients nowadays.

In The Netherlands, provocative tests as GHRH or arginine alone, arginine combined with clonidine, clonidine alone, exercise test, or L-Dopa combined with propranolol are currently only used in a very limited number of patients. These tests are mainly used in patients with CO-GHD who are retested when reaching adulthood by internists (GHRH or arginine alone) or by pediatricians (other previously mentioned tests). The apparent unpopularity of these tests is in accordance with a recent study, in which the relative use of six methods of testing for adult GHD is evaluated, showing that the ITT and the GHRH–arginine test are
indeed the most reliable tools to diagnose severe GHD in adults (16).

Although the ITT is considered the ‘gold standard’ in diagnosing GHD in adults, this test is contraindicated in patients with ischemic heart disease or seizure disorders (11, 26). The GHRH–arginine test is considered to be a reliable alternative during the whole lifespan with fewer side effects than the ITT, and it is preferred over an ITT by patients as well (16, 24, 27, 28). This contributed to the shift from ITT toward the GHRH–arginine test as the test of first choice.

In summary, this is the first publication of data of the Dutch National Registry of GH Treatment in Adults, which is a large nationwide surveillance database containing almost 2900 patients with severe GHD at January 2009. The database is of additional value in the research of long-term effects and safety of GHT in adults with severe GHD. Not only data of patients treated with GH but also follow-up data of a primary and a secondary control group are registered. Furthermore, the Dutch National Registry of GH Treatment in Adults is financed by the Health Care Insurance Board and therefore independent of pharmaceutical companies. The baseline patient characteristics are comparable to that of other GH surveillance databases. In the majority of the patients, the diagnosis of severe GHD was established by provocative testing, particularly an ITT or a combined GHRH–arginine test, with an evident increase in percentage of GHRH–arginine tests being performed in the last few years.

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.

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