CLINICAL STUDY

Incidence of GH deficiency – a nationwide study

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Abstract

Objective: Data on incidence rates are scarce in GH deficiency (GHD). Here, we estimate the incidence rate in childhood onset (CO) and adult onset (AO) GHD in Denmark.

Design: We used three national registries to identify 9131 cases with an increased risk of GHD. Date of entry was defined using the date when a registration had taken place and when a date of sufficient information could be defined from a thorough examination of a record of a GHD patient, which ever came last. We considered date of entry as the incident date.

Methods: Sex-specific incidence rates of GHD in children and adults using the background population as reference.

Results: During 1980–1999, 1823 patients were incident. Three-hundred and three males and 191 females had CO, 744 males and 585 females had AO GHD. The incidence rate over time was stable for females with AO GHD and increasing for the other three subgroups. Average incidence rate for CO males, 2.58 (95% confidence interval (CI), 2.30–2.88), CO females, 1.70 (95% CI, 1.48–1.96), AO males, 1.90 (95% CI, 1.77–2.04), and AO females, 1.42 (95% CI, 1.31–1.54) all per 100 000. The incidence rate was significantly higher in males compared to females in the CO GHD group ($P < 0.001$) and in the AO GHD group in the age ranges of 45–64 and 65+ years ($P < 0.001$). There was no significant difference in the 18–44 years age group.

Conclusions: In conclusion, we have identified the incidence rates of GHD in a nationwide study of Denmark. In this population-based study, we have identified in CO GHD and in the two oldest age groups of AO GHD, a statistically significant higher incidence rate in males when compared with females.

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Introduction

The interest in the epidemiology of growth hormone deficiency (GHD) derives from the increasing focus on patients with GHD during the last decades. This interest was spurred on by the finding of positive changes in body composition in patients with GHD being treated with growth hormone (GH) (1–4). GH substitution is expensive and potentially of life-long duration and reliable epidemiologic data to assess the size and turnover of the patient population are important.

There are few data on incidence rates of GHD. Childhood onset (CO) GHD has been estimated to occur in 1 per 30 000 people per year (5). In adult onset (AO) GHD, an annual incidence of 1.2 per 100 000 adults has been estimated (6). To our knowledge, there have been no nationwide studies using uniform diagnostic and classification criteria for all citizens.

Consensus reports for diagnosing GHD in children (7) and adults (8) have facilitated a more uniform diagnostic

approach worldwide. However, there is still no standardized approach to the diagnosis of hypopituitarism, which impedes epidemiologic assessment, and necessitates a definition of GHD, which can be applied currently as well as previously. This problem is reflected by the variability of criteria applied in previous epidemiologic studies.

Here, we present data linking personal hospital records with data from national registries, enabling a comprehensive coverage of an entire population. We utilized the Cancer Registry (CR), the National Patient Registry (NPR), and the Causes of Death Registry (CDR), as well as the Central Office of Civil Registration (OCR) for information on vital status.

Materials and methods

To identify all cases of possible GHD in Denmark, we used the unique Danish registries. Three registries identified the primary cohort; CR, which registers

patients in Danish hospitals with a cancer diagnosis; NPR, which registers all in-patients and, since 1995, all out-patients; and CDR, which registers the cause of death in all deceased patients. As all Danish citizens from 2nd of April 1968 were given a unique identification number (Central Person Registrations (CPR)-number) from OCR, it is possible from the various registries to identify all patients registered and to ensure a one-to-one coding within and between the registries. Foreigners are given a CPR-number including their initials, thus clearly differentiating these from Danish CPR-numbers. The total number of citizens in Denmark in 1980 was 5 122 065, and in 1999, it was 5 313 577 (Source: Statistics Denmark).

CR was founded in 1942 by The Danish Cancer Society, and received on voluntary basis information about cancer diseases in Denmark from 1943 until 1987 (Source: <http://www.sst.dk>). Hereafter, recording was compulsory. For all diseases, the cases' CPR-number was recorded with topography and morphology of the tumor, when available. The codes used are all translated into The International Classification of Diseases 7th edition (ICD-7). The registration in CR is generally for malignant tumors, but for some tumors, including cerebral tumors, registration includes benign tumors as well. Furthermore, the hospital in which the

patient was diagnosed has been recorded with a code uniquely assigned to each hospital in Denmark. We applied for the following topography: the pituitary gland, the ductus craniopharyngei and the pineal gland, and both benign and malignant morphology.

NPR was founded in 1977. Diagnoses for all patients are registered using ICD-8 until 1993, hereafter ICD-10, codes for hospitals are registered, and all is linked to the CPR-number. In NPR, we searched for all hospital activities coded at least once with one or more of 31 diagnoses of interest (Table 1).

In 1970, CDR was founded and registration was compulsory from the outset. Here, up to four causes of death as well as non-lethal chronic diseases are registered, linked to the CPR-number. Furthermore, the code for an eventual hospital is registered. CDR used ICD-8 until 1993, hereafter ICD-10. From CDR, we identified the cases having the diagnoses 253.19, 253.13 (both ICD-8), and DE23.0 and DE34.3 (both ICD-10) (for further details, see Table 1).

The cases from CR, NPR, and CDR, all had a relatively high *a priori* risk of having GHD. To identify the patients with GHD, we visited all departments, including psychiatric wards, in Denmark where the CPR-numbers had been registered. Most were Departments of Medicine or Endocrinology, Pediatrics, or Neurosurgery.

Table 1 Diagnoses in the national patient registry used to identify part of the primary cohort.

Diagnosis	
<i>ICD-8</i>	
194.39	Malignant neoplasm of the pituitary gland and the craniopharyngeal duct
194.49	Malignant neoplasm of the pineal gland
226.20	Malignant neoplasm of the pituitary gland
226.21	Benign neoplasm of the craniopharyngeal duct
226.29	Benign neoplasm of the pituitary gland and the craniopharyngeal duct
226.39	Benign neoplasm of the pineal gland
253.10	Hypopituitarism after therapy
253.11	Necrosis of the pituitary gland (postpartum)
253.12	Adiposogenital dystrophy
253.13	Pituitary dwarfism
253.18	Hypopituitarism, unspecified
253.19	Hypopituitarism
253.29	Chromophobic pituitary adenoma
253.99	Disorders of the pituitary gland, unspecified
258.01	Basophilic pituitary adenoma
258.90	Dwarfism, unspecified
<i>ICD-10</i>	
DC75.1	Malignant neoplasm of the pituitary gland
DC75.2	Malignant neoplasm of the craniopharyngeal duct
DC75.3	Malignant neoplasm of the pineal gland
DD35.2	Benign neoplasm of the pituitary gland
DD35.3	Benign neoplasm of the craniopharyngeal duct
DD35.4	Benign neoplasm of the pineal gland
DD44.3	Neoplasm of uncertain or unknown behavior of the pituitary gland
DD44.4	Neoplasm of uncertain or unknown behavior of the craniopharyngeal duct
DE23.0	Hypopituitarism
DE23.1	Drug-induced hypopituitarism
DE23.6	Other disorders of the pituitary gland
DE23.7	Other disorders of the pituitary gland, unspecified
DE34.3	Short stature, not elsewhere classified
DE89.3	Postprocedural hypopituitarism
DZ90.8	Acquired absence of other organs

The visits started 17 May 2002 and ended 25 June 2004. More than 100 hospitals or city archives were visited, and the investigations at the departments were carried out by two investigators. All departments with registrations gave permission to read the records.

Criteria for the diagnosis GHD were chosen based on published guidelines (7,8) with modifications (9–11), see Table 2. If necessary two or more departments were

visited in order to find relevant and sufficient data about each case. All records were studied first at the hospitals with specialized departments (i.e. pediatric, neurosurgical, or endocrine departments) thereafter at hospitals without specialized departments. Definitive disproof of the diagnosis of GHD was followed by a non-GHD status; otherwise the record was studied at other departments until the status of GHD was either disproved or

Table 2 Criteria for the diagnosis of growth hormone deficiency (GHD) divided into subgroups childhood onset (CO) and adult onset (AO).

Criteria for GHD diagnosis	CO (less than 18 years at onset)	AO (18 years or more at onset)
	Two positive stimulation tests, or one positive stimulation test and insulin-like growth factor-I (IGF-I) <2 s.d., or one positive stimulation test and documented insufficiency of one hormone, or one positive stimulation test and pituitary irradiation, or one positive stimulation test and pituitary pathology (computerised tomography (CT) or magnetic resonance imaging (MRI) scan), or one positive stimulation test and verified genetic defect resulting in GHD, or one positive stimulation test and growth retardation, or growth retardation and documented insufficiency of one hormone, or growth retardation and pituitary irradiation, or operation on the pituitary and documented insufficiency of one hormone, or operation on the pituitary and pituitary irradiation, or pituitary irradiation and documented insufficiency of one hormone, or relevant clinical diagnosis*	Two positive stimulation tests, or one positive stimulation test and documented insufficiency of one hormone, or IGF-I <2 s.d. and documented insufficiency of one hormone, or operation on the pituitary and pituitary irradiation, or operation on the pituitary and documented insufficiency of one hormone, or two pituitary operations, or documented insufficiency of two hormones, or pituitary pathology (CT or MRI scan) and documented insufficiency of one hormone, or pituitary irradiation (>5 years) and documented insufficiency of one hormone, or relevant clinical diagnosis*
Criteria for each test		
Accepted tests	Insulin tolerance test (ITT), arginine and growth hormone-releasing hormone (GHRH), arginine, clonidin, glucagon, L-DOPA, and heat exposure	ITT, arginine and GHRH, pyridostigmin and GHRH, arginine, glucagon, heat exposure
Adrenocorticotropin (ACTH)	Synachten or ITT <550 nmol/l after 30 min. If a department had a well defined and different cut-off, this value was used Metyrapone test followed by a clinical interpretation of insufficiency Blood samples followed by a clinical interpretation of insufficiency	Same
Follicle-stimulating hormone/luteinizing hormone (FSH/LH)	FSH/LH below relevant reference Females: estrogen below relevant reference followed by clinical interpretation of insufficiency Amenorrhea followed by clinical interpretation of insufficiency Males: testosterone below relevant reference Secondary sexual development insufficient	Same, and luteinizing hormone-releasing hormone-test followed by a clinical interpretation of insufficiency FSH/LH below relevant reference (postmenopausal) followed by a clinical interpretation of insufficiency Loss of libido followed by a clinical interpretation of insufficiency
Thyrotropin (TSH)	T4 below relevant reference T4 within reference followed by a clinical interpretation of insufficiency	Same
Anti-diuretic hormone	Insufficient response during water deprivation test Clinical interpretation of insufficiency combined with successful medical treatment for more than 3 months	Same
Growth retardation	Height >3 s.d. below mean Height >1.5 s.d. below expected parental height Height >2 s.d. below mean and reduced by >0.5 s.d. during 1 year among children more than 2 years of age Change in height >2 s.d. below mean for 1 year Change in height >1.5 s.d. below mean for 2 years	Irrelevant

*History of pituitary apoplexy, craniopharyngeoma, empty sella, Sheehan's syndrome, trauma, pituitary bleeding, GHD combined with history of medical substitution.

confirmed. If the status of GHD could not be confirmed at any department, the case was considered non-GHD. When in doubt, relevant information from the record was discussed with two trained endocrinologists. It is important to stress that the diagnosis of GHD was only applied when the clinical context was relevant.

In describing the cohort, the following dates are of importance: (i) Date of onset represents the estimated date the patient became deficient on the GH axis; (ii) Date of sufficient information represents the date when date of onset was notified in a record; and (iii) Date of registration represents the first date when the patient is noted in any register; (iv) For each patient, a date of entry of GHD was defined using: (i) the date of first registration in the registry or (ii) the date of sufficient information, whichever came last. It is necessary to use the latest date since patients must be both registered to enter the primary cohort of possible cases, and the record must contain sufficient information to ensure a correct diagnosis of GHD. The entry date is considered as the incident date and does not necessarily represent a diagnosis at the hospital, since only some of the patients were formally tested for GHD at any department. For instance, a patient born on 1 January 1940, who becomes GH deficient from 1 February 1950, and has sufficient information in a record on 1 March 1981 and a registration on 1 May 1982 will be defined as CO GHD. This patient is 10.1-year old at onset of disease, has sufficient information to ensure the diagnosis at the age of 41.2, and is identified in the registry at the age of 42.3. Thus, the patient is considered incident on date of entry, 42.3 years of age, as CO GHD.

The criteria for GHD were divided into two groups according to age at onset: CO, children younger than 18 years; AO, patients of 18 years or more at onset. The diagnosis 'CO GHD' was permanent no matter what the current age is.

Ethical aspects

The study was approved by The Danish Data Protection Agency, The Research Ethics Committee, and Doctors' Counsel in The Danish National Board of Health.

Statistical analysis

For most calculations, our data were divided into four categories: CO, males and females, and AO, males and females. We used The Statistics Denmark to obtain the information about number of citizens by gender in different age groups in the Danish population. In each category, incidence rates were calculated by the total number of new entries per calendar year divided by the corresponding number of citizens (same age group, same gender) per 1 July the relevant year, times 100 000. Incidence rates were analyzed using Poisson regression, and confidence limits using an approximation to Poisson distribution. The differences in gender distribution in

various subdiagnoses were analyzed using incidence rate ratios. $P < 0.05$ was considered significant. All analyses were performed using Intercooled Stata 8.2 (StataCorp; College Station, TX, USA).

Results

Ascertainment of the primary cohort

CR, NPR, and CDR. CR identified 4605 registrations (Fig. 1). Two-hundred and thirty-one had a CPR-number, which either implied that the case was a foreigner or was registered before the initiation of the CPR-number system, making it impossible to localize the record. The code for the hospital was lacking in 35 and multiple reporting happened in 1924 registrations. These registrations were excluded. In total, 2415 cases were included from CR. NPR identified 14 112 registrations, 96 were of foreign origin, and 5332 had multiple reports, making a total of 8684 cases. In CDR, 118 registrations were identified. Forty-six did not have a registration at a hospital, making a total of 72 cases. In summary, 2415, 8684, and 72 cases were identified in CR, NPR, and CDR respectively representing 9131 unique cases. Eight-hundred and ninety-eight cases' records could not be found at any department. Based on the available records, 2263 patients with GHD were identified, corresponding to 27.5% of all cases identified *a priori* as having a high probability of having GHD and whose record was found. Using OCR 58 patients were excluded because their municipality code at diagnosis was Greenland, unknown, or an administrative code. We focused on patients with date of entry after 1980 to ensure enough run-in time from 1977 when NPR was founded, the registry where the majority of patients were identified. The end of the study period was 1999, as this year was the last year of registration in the registries. All other patients were excluded from the present analysis, including 336 patients with entry before 1980 and 44 patients after 1999. Two patients were excluded due to an error at registration. Thus, the final number of patients identified was 1823. For further information on the identification of the cohort, see Fig. 1, and for further information on the patients, see Table 3. All but ten patients were identified in NPR; the ten patients were exclusively identified in CR, and none exclusively in CDR.

For data quality assessment, we searched the archives in one department (Medical Department M, Aarhus Sygehus, Aarhus University Hospital), to identify potentially missed patients. One-hundred and sixty-eight patients treated with GH were identified. Nine patients were not included in our search from the registries, of these six patients did not have GHD, but were treated with GH for other reasons such as Turner syndrome, Prader Willi syndrome, etc. and only three

Figure 1 Flow chart of the identification of the final study population of patients with growth hormone deficiency (GHD), identifying the number of records and cases localized in the three registers.

patients had GHD. In other words, of 162 eligible patients, 3 were not identified in our search in the three registries.

Incidence

Figure 2 shows the incidence rates of GHD by sex and age at onset of disease in Denmark from 1980 to 1999.

The average incidence rates, the changes in incidence rates over time, as well as the incidence rate ratios for the two genders are described in Table 4. Since we observed a change in incidence rates over time, we included this change in the calculation of incidence rate ratios. Furthermore, we merged all the different diagnoses into nine subgroups (Table 5). The total incidence rate for CO males was significantly higher than females, whereas

Table 3 Characteristics of patients with GHD. Patients were divided in CO and AO GHD, discriminated by an age cut-off of 18 years at onset. Onset is when the patients became GH deficient, entry corresponds to incidence, and delay is the difference between entry and onset (see Materials and Methods section for further information on the definition of onset, entry and delay).

	CO males	CO females	AO males	AO females
Number of patients	303	191	744	585
Median age and range at onset (years)	9.1 (0.0–18.0)	8.6 (0.0–18.0)	51.3 (18.1–91.3)	49.4 (18.0–94.6)
Median age and range at entry (years)	13.5 (0.1–77.0)	12.9 (0.1–78.8)	57.2 (18.1–91.3)	55.8 (18.5–87.7)
Median delay and range (years)	1.0 (0.0–61.0)	1.2 (0.0–62.4)	0.2 (0.0–48.8)	0.3 (0.0–56.2)

there was no significant difference in incidence rate for males and females in CO GHD in the nine subgroups possibly due to lack of power (data not shown). For AO GHD, we found in total and in two subgroups, namely ‘nonfunctioning adenoma’ and ‘other adenomas’, an overall significantly higher incidence rate ratio for males compared with females (data not shown). We divided AO GHD into three age groups: less than 45 years, 45–64 years, and more than 65 years at entry, and calculated incidence rate ratios (data not shown). In total, in the two oldest age groups, the incidence rate was significantly higher among males compared to females. Similarly, the incidence rate was significantly higher among males compared to females in the two oldest age groups in ‘nonfunctioning adenoma’; in ‘other adenomas’ this was only in the oldest age group.

Discussion

We have determined the incidence rates of CO and AO GHD in an entire population. Uniform criteria have been applied to all cases ensuring an accurate and unbiased approach to the identification of potential patients. We identified significantly more males than females, both in CO and in subgroups of AO GHD. In previous epidemiologic studies of CO GHD, this has been described, but to our knowledge it has not been described before in a population of AO GHD. We identified two specific diagnoses (‘nonfunctioning adenoma’ and ‘other adenomas’) with a significantly different sex distribution. The higher number of men with GHD, and especially with AO GHD, merits further investigation.

Figure 2 Incidence rate of GHD per 100 000 citizens (gender specific). The denominator for childhood onset GHD was number of citizens less than 18 years, and for adult onset GHD it was number of citizens aged 18 years or more. Note different scales.

Table 4 Patients with GHD, details and results.

Age at onset	Sex	Number of patients	Percentage tested for GHD	Average incidence per 100 000	Incidence 95% CI	Average incidence per 100 000*	Incidence 95% CI	Annual change in incidence rate†	Incidence rate 95% CI	P-value	Incidence rate ratio‡	Incidence rate ratio 95% CI
<18, CO	Males	303	73.3	2.58	(2.30–2.88)			1.05	(1.03–1.07)	<0.001		
<18, CO	Females	191	73.8	1.70	(1.48–1.96)	2.15	(1.97–2.35)	1.03	(1.01–1.06)	<0.05	1.51	(1.26–1.81)
≥18, AO	Males	744	30.0	1.90	(1.77–2.04)			1.02	(1.00–1.03)	<0.05		
≥18, AO	Females	585	29.7	1.42	(1.31–1.54)	1.65	(1.57–1.75)	1.01	(0.99–1.02)	0.45	1.33	(1.20–1.49)
Total	Both	1823	41.7	1.76	(1.69–1.85)	1.76	(1.69–1.85)	1.02	(1.01–1.03)	<0.001	1.39	(1.26–1.52)

CI: confidence interval.

*Average incidence rates, both gender.

†The factor the incidence rate changes annually.

‡The incidence rate for males compared to the incidence rate for females for CO (less than 18 years of age at onset), AO (18 years of age or more at onset), and total.

We observed an increase in incidence over time for all subgroups, except females with AO GHD. It seems reasonable to consider the incidence in males with CO GHD as two stable incidences from 1980 to 1986 and from 1987 to 1999, with a change in 1987 (see Fig. 2). In the late 1980s, recombinant human GH became available on the market for children with GHD, and the change in 1987 might reflect this fact. A similar, but less profound, change can be observed in females with CO GHD from 1986 to 1987. We expected to find an increase in incidence as focus on GHD has increased with numerous publications on the metabolic changes in patients with GHD, and the benefits of treatment with GH. An increased clinical awareness is a possible contributing cause for this increase in incidence. The finding of an average incidence rate of 1.65 per 100 000 for AO GHD is higher than, but in agreement with, the finding of 1.2 per 100 000 in a French study (6), and the estimate of 1.0 per 100 000 from The Growth Hormone Research Society (12). The denominator in the latter study was not specified, and it is thus not clear whether the estimate is age-specific or based on the total population. For the interpretation of the present data, it is important to note that a patient is defined as incident at the date of entry in a registry combined with sufficient data to define the patient as having GHD, which may, to some extent, delay the true date of incidence of GHD.

The observed heterogeneity of diagnoses causing GHD is somewhat surprising. This could imply that clinicians should be aware of the possibility of GHD in patients with various syndromes, systemic disorders, hematological diseases, etc. A further analysis is warranted to classify why some pituitary adenomas lead to more cases with GHD among males in the older age groups. Since our definition of GHD is partly based on the presence of other pituitary deficits, a gender difference in the diagnosis of these deficits could translate into differences in the estimated incidence of GHD. It is likely that gonadotropin deficiency is underdiagnosed in postmenopausal women relative to age-matched males, but we do not consider this as a sufficient explanation for the skewed gender distribution of GHD. Furthermore, we speculate that the function of the pituitary, and in particular the secretion of GH, might be more vulnerable in men than in women, resulting in a lower threshold for GHD after a comparable event. In Denmark, the general practitioner (GP) is the gatekeeper to the hospital for most patients. Women have significantly more visits at the GP than men (Source: Statistics Denmark), but we believe that the GP refer men to the hospitals as easily as they do women. In this regard, it could be speculated whether women with pituitary adenomas are diagnosed earlier with a smaller tumor, thus reducing their risk of postoperative hypopituitarism. From the Danish Pituitary Registry, we know that the ratio of number of operations on pituitary adenomas among males and

Table 5 Diagnoses causing GHD.

Diagnosis	Males CO	Females CO	Males AO	Females AO	Total
Non-functioning pituitary adenoma	5	2	239	133	379
Hormonally active pituitary adenoma, (subtotal)	6	4	94	89	185
ACTH	1	2	29	38	70
GH	0	0	3	1	4
FSH/LH	0	0	6	3	9
TSH	0	0	0	3	3
Prolactin	3	2	28	14	47
N/S	2	0	28	22	52
Other pituitary adenomas (subtotal)	4	3	131	91	229
Hemorrhage in adenoma	1	1	56	36	94
N/S	3	2	75	55	135
Craniopharyngeoma	30	20	55	53	158
Idiopathic hypopituitarism	38	19	0	0	57
Benign tumors in/close to the pituitary (subtotal)	50	27	37	35	149
Germinoma	14	3	8	2	27
Astrocytoma	18	12	1	3	34
Others*	18	12	28	30	88
Malignant tumors (subtotal)	19	16	28	16	79
Acute lymphoblastic leukaemia	3	2	1	1	7
Cancer of rhinopharynx	0	0	3	2	5
Lymphomas	2	1	4	1	8
Malignant adenoma/pinealoma/germinoma	4	4	7	4	19
Medulloblastoma	9	6	1	0	16
Metastases	0	0	7	7	14
Others†	1	3	5	1	10
Others (subtotal)	93	58	122	146	419
Aneurysm	0	0	1	4	5
Aplasia/hypoplasia of the pituitary	18	15	3	6	42
Apoplexy of the pituitary	0	2	11	16	29
Birth trauma	11	1	0	0	12
Cysts‡	5	2	16	10	33
Empty sella	1	2	7	7	17
Encephalitis/meningitis/hypophysitis	0	0	5	2	7
Granulomatous inflammation	4	1	4	4	13
Irradiation	4	0	11	8	23
Neurofibromatosis recklinghausen	4	6	0	0	10
Postoperative hypopituitarism	1	3	21	11	36
Sheehan syndrome	0	0	0	31	31
Syndromes	6	2	1	2	11
Trauma	6	3	8	3	20
Others	33	21	34	42	130
Unknown	58	42	38	30	168
Total	303	191	744	585	1,823

CO: childhood onset (less than 18 years at onset), AO: adult onset (18 years or more at onset).

*Angiofibroma, cholesteatoma, chordoma, ependymoma, glioma, hemangioma, hygroma, giant-cell tumour, meningioma, neurocytoma, pineocytoma, teratoma, or N/S.

†Carcinoid tumour, embryonal carcinoma, or rhabdomyosarcoma.

‡Arachnoidal, colloid, congenital, epidermoid, or N/S. N/S: not specified.

females is 1 (13), but we lack information about the actual size of the adenoma. Thus, we have limited data to support this hypothesis, but it could be of interest to study gender-specific differences in tumor morphology at the time of diagnosis. It is important to stress that the entity of GHD is heterogeneous, with many patients included because a primary disease caused GHD, and that data with a skewed gender distribution does not imply for instance that more males than females have a nonfunctioning adenoma, but that within the group of nonfunctioning adenomas more males than females become GHD.

Applying this design for identifying cases will necessarily overlook potential cases. First of all, some

records could not be found (representing 898 cases), possibly overlooking 247 patients with GHD (27.5% of the included high risk population had GHD). These potential patients were generally older than the identified patients (data not shown), they might not have entry during 1980–1999, and 247 patients might be an overestimation. Secondly, a broader search for more diagnoses that could result in GHD when using the registers would probably have included more cases and expanded the primary cohort markedly hereby finding more patients with GHD. But the yield would presumably have been small, because more diagnoses would probably have included a relatively small number

of extra patients, and importantly, would have made it impossible to complete the project. Thirdly, patients who are registered incorrectly, who have atypical diagnoses without relevant clinical and biochemical investigation of their pituitary function, or who never reached a hospital are not identified. The size of this group is unknown, and these patients cannot be found unless a nationwide study of all Danish citizens is undertaken. All of these parameters tend to underestimate the incidence rates at all times.

Since the codes in NPR have only included out-patients since 1995, patients seen only as out-patients before 1995 have not been identified. Most patients with GHD have often at one stage been admitted as in-patient and therefore identified at this stage. Some cases, who are suspected of having GHD, are obviously not admitted as in-patients, but we believe that the *a priori* risk of GHD in these cases is lower than those who are admitted. The potential loss of patients is, therefore, minimal. There is no possible way of identifying these patients, applying the current approach to all departments. Departments with special interest in endocrine problems sometimes have lists of patients who are treated with GH. We did not use these lists to identify the patients, as this information would be distributed unequally among the departments. We used some of these lists to quantify the number of cases not identified from the registries. The general experience was that only a few patients were not identified and that these patients generally had rare diagnoses such as rhabdomyosarcoma of the ear or had been diagnosed recently. We conclude that the presented approach is the best possible for identifying patients with GHD as we used the same strategy nationwide to identify patients, and the potential loss of patients is reasonably small.

The use of a general search in the Danish population at all hospitals ensures that most patients with a GHD diagnosis are being identified. However, we believe that substantial numbers of people suffering from endocrine diseases, and in particular GHD, are still being withheld from the referral hospitals for various reasons. We identified these patients using the present design, but as seen in screening of elementary-school children (14–16) about half of the children had unrecognized GHD and cannot be identified. However, we identified most of the patients who had been referred to any hospital at any time, and thus were suspected of suffering of GHD. Recently, however, traumatic head injury (TBI) has been suggested as a cause of diminished pituitary function, and consensus guidelines describe how to deal with the patients suffering from TBI (17), but the clinical awareness concerning TBI during our study period must be considered reduced compared with present awareness. Thus, we may have missed some patients with TBI-induced GHD.

All but ten patients were identified in NPR, which was founded in 1977. For the following years, most patients will be registered for the first time, either as an incident

patient or during a follow-up regimen. The registration does not discriminate between new or known patients. As we define our cohort by number of patients with entry after 1 January 1980, we do not include the first 3 years of registration. A potential overestimation of incidence in 1980 is considered negligible. As we started studying the records on 17 May 2002, ample time to perform analyses of eventual tests from 1999 is ensured.

We included patients in our cohort where the clinical history without any diagnostic tests of GHD was in favor of GHD. Historically, enormous changes have taken place in the identification of patients with GHD. In the beginning of the study period, certain criteria were considered gold standard, criteria which would not be used presently to diagnose any patient. For some of the patients, we are dependent on past criteria in order to determine whether the patient had GHD as often no other data exist. Here lies a possibility of including patients without GHD, but we consider the potential loss of data if not including these patients as introducing an even greater bias.

In conclusion, we have identified the incidence of GHD in a nationwide study. We found that the incidence rate was increasing among CO, males and females, and AO males, whereas it was stable for AO females. Significantly more males than females were identified, which applies to CO GHD as well as subgroups within AO GHD, namely nonfunctioning pituitary adenoma and other pituitary adenoma. The latter finding merits further investigation.

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