The epidemiology of pituitary adenomas in Iceland, 1955–2012: a nationwide population-based study

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Abstract

Objective: Pituitary adenomas (PA) are among the most common human neoplasms. To describe the epidemiology and assess the disease burden of clinically significant PAs, population-based studies are needed. Iceland has a small well-defined population. The aim of this study is to describe the epidemiology of PAs in Iceland over an expanded period of time.

Design: This is a retrospective observational study, including all PAs diagnosed in Iceland from 1955 to 2012.

Methods: Extensive clinical information was gathered in a database. Prevalence rates for all PA subtypes were calculated along with standardized incidence rates (SIR). Sex ratios and relationships with adenoma size, age, and symptoms were assessed.

Results: We identified 471 individuals: 190 men and 281 women. Total prevalence in 2012 was 115.57/100 000, prolactinomas were most prevalent (54.37/100 000) followed by non-functioning adenomas (NFPAs) (42.32/100 000). Throughout the period, NFPAs were most common (43.0%) followed by prolactinomas (39.9%) and 11.3% had acromegaly and 5.7% Cushing's disease. Women are diagnosed younger with smaller adenomas. Total SIR has increased significantly and is now 5.8/100 000 per year.

Conclusion: In this nationwide study spanning six decades, we have confirmed PAs rising prevalence and incidence rates noted in recent studies. We demonstrated higher overall prevalence and incidence rates than ever previously recorded with an increasing predominance of NFPAs, which is not explained by incidental findings alone. There is a relationship with the introduction of imaging modalities, but the vast majority of patients are symptomatic at diagnosis. This underlines the importance of increased awareness, education, and appropriate allocation of resources for this growing group of patients.

European Journal of
Endocrinology
(2015) 173, 655–664

Introduction

Pituitary adenomas (PAs) are usually indolent and benign. They can be associated with hormonal hypersecretion, local mass effect, hypopituitarism, and

adverse results of therapy causing significant morbidity (1, 2, 3, 4, 5). A proportion is still asymptomatic and remains undetected.

The interpretation of earlier epidemiology data on PAs is challenging, and it is only within the last decade that more intensive population-based studies have begun to emerge enabling assessment of their true disease burden and associated costs. Some studies report prevalence data (6, 7, 8, 9) and a few report incidence rates (8, 10). These studies indicate a rise in both prevalence and incidence. It may remain uncertain whether some of the results of these studies are related to specific populations, genetics, areas, or time periods. The addition of this comprehensive longitudinal analysis based on a homogenous population may help confirm and clarify some of these points.

Iceland has a small, well-defined population with access to extensive clinical data over an extended period of time. This provides a unique opportunity for in-depth epidemiological studies. The aim of this study is therefore to define the prevalence and incidence rates of all types of PAs in Iceland over the last 58 years, explore possible contributing factors to rate variations, and compare with other recent population-based epidemiological data.

Subjects and methods

Study population

Iceland is an island in the middle of the North Atlantic Ocean with a growing population of ~330 000 people with a limited immigration for the last few centuries. Icelanders have kept a unique and accurate set of genealogical records since the time of first settlement in the late ninth century (11). Iceland has a national health service, and patients requiring investigations or treatment for suspected pituitary disease will be seen at a limited number of facilities from which there is relatively easy access to extensive clinical information. All patients diagnosed with a PA at any site in Iceland during the period of 1955–2012 were included in the study. Considering the defined nature of the extensive data available, the whole Icelandic population provides a suitable background for the purpose of this analysis. Information about the exact population size at different times (Table 1) was obtained from Statistics Iceland (Hagstofa Islands).

The study was approved by the Icelandic Data Protection Authority and Icelandic National Bioethics Committee.

Data gathering

A database recording all instances of PAs in the total population of Iceland during 1955–2012 was constructed. Information was obtained from medical records at the National University Hospital of Iceland and the three district general hospitals in Iceland, from the records of all privately practicing endocrinologists and gynaecologists in the country, the Icelandic Cancer Registry, the department of pathology, all four radiology departments in the country, and the Icelandic Heart Association (IHA). IHA has conducted studies focusing on multiple causes of disability, including cerebrovascular disease and Alzheimer's, which include cranial imaging where a few PAs were initially diagnosed. Initial search criteria were broad to include a range of endocrinological- and CNS-related diagnoses to minimise a change of missed cases (ICD-10: D33, D35, D43, D44, E22, E23, E24, E29, E31, E34, E35). Each case was reviewed and the diagnosis of a PA was confirmed by a consultant endocrinologist where appropriate. All diagnoses were verified by at least two consultant endocrinologist through scrutinizing clinical, hormonal, pathological, and imaging data. The data recorded included diagnosis, gender, age at diagnosis, presenting symptoms, adenoma size, findings on imaging, biochemical findings prior to and following treatment, details of medical and surgical treatments, histopathological findings (including immunohistopathological staining, invasiveness, and markers of proliferation and atypia), and details of follow-up. The database is incorporated into the patient record system at the National University Hospital of Iceland.

Adenoma subtypes were classified according to hormonal secretion. All adenomas with no evidence of hormonal hypersecretion were defined as non-functioning pituitary adenomas (NFPAs). Prolactinomas were defined as adenomas associated with hyperprolactinaemia (above local reference ranges defined by sex), whereas all other causes had been considered and eliminated, including stalk compression. Patients with hyperprolactinaemia and

Table 1 Changes in total prevalence rates and age SIR of pituitary tumours in Iceland from 1955–2012.

Period	1955–1972	1973–1982	1983–1992	1993–2002	2003–2012
Total population at end of period	210.912	235.538	262.386	288.471	321.857
Live patients at end of period	14	35	70	208	372
Prevalence (per 100 000)	6.63	14.86	26.68	72.10	115.57
SIR (per 100 000 per year) (95% CI)	0.6 (0.3–0.9)	1.3 (0.8–1.8)	2.5 (1.9–3.1)	4.4 (3.6–5.1)	5.8 (5.0–6.6)

negative imaging results were only included if they fulfilled all of the following criteria: hyperprolactinaemia, symptoms of hyperprolactinaemia, symptomatic and biochemical response to treatment with dopamine agonist. All other causes had been considered and eliminated (14 patients in total). Acromegaly or Cushing's disease was confirmed based on clinical presentation and biochemical evidence according to international guidelines and consensus statements (12, 13, 14), along with consistent histopathological findings for those patients who underwent surgery. No thyroid-stimulating hormone-producing adenomas have been diagnosed in Iceland. Adenomas measuring 10 mm or more in their greatest diameter were classified as macroadenoma, and adenomas <10 mm as microadenoma. An adenoma was defined as being discovered incidentally if found during investigations for which pituitary disease could not have been an indication. For the purpose of longitudinal analysis, the total period was divided into five time periods allowing enough patients in each group to power statistical analysis (1955–1972, 1973–1982, 1983–1992, 1993–2002, 2003–2012). In this paper, the terms 'final prevalence' and 'final standardized incidence rate (SIR)' apply to calculated prevalence on the 31 December 2012 and SIR applying to the period 2003–2012 respectively.

Statistical analysis

The prevalence of PAs in general, and for each subtype, was calculated by dividing the number of patients with the total population at risk (population of Iceland) for each period and reported as cases/100 000 inhabitants.

Crude incidence rates were standardized against the World Health Organization 2000 standard population (15). The direct method was used and all reported incidence rates are standardized (SIR) and quoted as cases/100 000 per year. Using the Wilson's method, 95% CIs were calculated. Associations between categorical variables were analysed using contingency tables and applying the χ^2 and Fisher's exact test. A two-sided $P < 0.05$ was considered significant. Statistical analysis and the generation of graphics was performed using the 'R' statistical language and environment (16).

Results

Prevalence

At the end of the study period (31 December 2012) the total population of Iceland was 321 857 inhabitants.

Given that 372 patients were alive, the final prevalence for PAs was 115.57/100 000. The final prevalence for women was 72.08/100 000 and men 43.49/100 000. Prolactinomas had the highest prevalence of 54.37/100 000 followed by NFPA (41.32/100 000), acromegaly (13.67/100 000), and Cushing's disease (6.21/100 000) (Table 2).

More detailed data on each subtype and prevalence data can be found in Tables 1 and 2 and in Fig. 1.

As shown in Table 1 the overall prevalence rate has risen from 6.63/100 000 in 1972 to 115.57/100 000 in 2012, mainly explained by a steep rise in diagnosis since around 1990 (Fig. 2).

All tumours diagnosed during 1955–2012

A total of 471 patients were identified during the period of 1955–2012 in the whole of Iceland: 190 were men (40.3%) and 281 women (59.7%). NFPA were the most commonly diagnosed adenomas (43.1%), followed by prolactinomas (39.9%), and acromegaly (11.3%). Cushing's disease was the least common (5.7%). NFPA was therefore the most common diagnosis over the whole period, but prolactinomas had the highest final prevalence rate (Supplementary Fig. 1A, see section on supplementary data and Supplementary Fig. 2 given at the end of this article).

More women had prolactinomas than men (M/F: 47/141; $P < 0.001$). Insignificantly more men presented with a NFPA than women (M/F: 104/99; NS). More men presented with acromegaly, but the difference did not reach statistical significance (M/F: 32/21; NS). Significantly more women were diagnosed with Cushing's disease (M/F: 7/20; $P < 0.05$) (Supplementary Fig. 1C, see section on supplementary data given at the end of this article and Table 2).

Macroadenomas were more common than microadenomas (54.8% vs 41.2%; $P < 0.05$). Macroadenomas present at a significantly higher age (median age, 54) than microadenomas (median age, 36) ($P < 0.001$); 60.1% of all macroadenomas were NFPA.

The majority of men presented with a macroadenoma (73.2% vs 43.2% for women $P < 0.001$), but the majority of women presented with a microadenoma (55.2% vs 20.5% for men $P < 0.001$) (Table 2). Due to old imaging techniques or imprecise autopsy results, 19 cases (4%) had an unknown adenoma size.

The median age at diagnosis for the whole cohort was 44 years (range: 4–94). Men presented at a significantly higher age than women (median age: 54 vs 37; $P < 0.001$). Patients with a macroadenoma also presented at a

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Table 2 Data on all pituitary adenomas diagnosed in Iceland from 1955 to 2012 and final data on prevalence.

	All adenomas	NFPA	Prolactinoma	Acromegaly	Cushing's
Total number of patients 1955–2012	471	203	188	53	27
Proportion of all adenomas (%)	100	43.1	39.9	11.3	5.7
Men (%)	190 (40.3%)	104 (51.2%)	47 (25.5%)	32 (60.4%)	7 (25.9%)
Women (%)	281 (59.7%)	99 (48.8%)	141 (75.0%)	21 (39.6%)	20 (74.1%)
Patients alive in 2012	372	133	175	44	20
Prevalence 2012 (per 100 000)	115.57	41.32	54.37	13.67	6.21
Men (per 100 000)	43.49	20.50	13.04	9.01	0.93
Women (per 100 000)	72.08	20.81	41.32	4.66	5.28
Median age at diagnosis (range)	44 years (4–94)	57 years (13–88)	35 years (13–94)	45 years (4–83)	42 years (12–76)
Men (range)	54 years (15–86)	61 years (17–86)	47 years (24–73)	45 years (15–83)	47 years (26–74)
Women (range)	37 years (4–94)	53 years (13–88)	32 years (13–94)	44 years (4–75)	40 years (12–76)
Macroadenoma (range)	54 years (4–88)	61 years (14–88)	42 years (15–85)	39 years (4–73)	51.5 years (33–76)
Microadenoma (range)	36 years (12–94)	44 years (13–84)	32.5 years (13–94)	48.5 years (39–83)	41 years (12–75)
Macroadenomas (% of total) ^a	258 (54.8%)	151 (74.4%)	68 (36.2%)	35 (66.0%)	4 (14.8%)
Men (%)	139 (53.9%)	89 (58.9%)	30 (44.1%)	20 (57.1%)	0 (0%)
Women (%)	119 (46.1%)	62 (41.1%)	38 (55.9%)	15 (42.9%)	4 (100%)
% of all men with macroadenoma	73.2%	85.6%	63.8%	62.5%	0%
% of all women with macroadenoma	42.3%	62.6%	26.7%	71.4%	20%
Microadenomas (% of total) ^b	194 (41.2%)	45 (22.2%)	118 (62.8%)	14 (26.4%)	17 (63.0%)
Men (%)	39 (20.1%)	11 (24.4%)	16 (13.6%)	9 (64.3%)	3 (17.6%)
Women (%)	155 (79.9%)	34 (75.6%)	102 (86.4%)	5 (35.7%)	14 (82.4%)
% of all men with microadenoma	20.5%	10.6%	34.0%	28.1%	42.9%
% of all women with microadenoma	55.2%	34.3%	72.3%	23.8%	70.0%
Incidental finding (% of total)	76 (16.1%)	62 (30.5%)	12 (6.4%)	1 (1.9%)	1 (3.7%)
Men (%)	35 (46.1%)	27 (43.5%)	6 (50.0%)	1 (100%)	1 (100%)
Women (%)	41 (53.9%)	35 (56.6%)	6 (50.0%)	0 (0%)	0 (0%)
Macroadenoma (%)	46 (60.5%)	36 (58.0%)	9 (75.0%)	1 (100%)	0 (0%)
Microadenoma (%)	25 (32.9%)	22 (35.5%)	3 (25.0%)	0 (0%)	0 (0%)

^aIt was not possible to confirm adenoma size in 19 cases. The sum of macro- and microadenomas is therefore not 100%.

^bPatients with negative imaging results were classified as having a microadenoma.

significantly higher age than those with a microadenoma (median age: 54 vs 36; $P < 0.001$). The median age at diagnosis has not changed significantly since the beginning of the study period (Table 2, Supplementary Fig. 2, see section on supplementary data given at the end of this article).

A minority of all adenomas were discovered incidentally (16.1%). There was no significant difference in numbers or prevalence of incidentally discovered adenomas between the sexes. Most were macroadenomas (60.5% vs 32.0% microadenomas; $P < 0.05$). The majority (81.2%) were NFPA and they represent 30.5% of all NFPA diagnosed: 15.8% were prolactinomas, 1.3% were acromegaly, and 1.3% Cushing's disease.

Incidence

The overall SIR rose significantly throughout the study period, from 0.6/100 000 per year for the period of 1955–1972 to 5.8/100 000 for the period of 2003–2012

(Table 1, Fig. 3). Since 1983 women have had a significantly higher overall SIR than men. For men, NFPA have always had the highest SIR, but prolactinomas have shown the highest SIR among women since 1973 (Supplementary Table 1, see section on supplementary data given at the end of this article, Fig. 3). Macroadenomas have always had a higher SIR than microadenomas among men, but since 1983 microadenomas predominate in women (Supplementary Table 2 given at the end of this article). The SIR for incidentally discovered adenomas rose throughout the period, but significantly less than for symptomatic adenomas. Their incidence and prevalence increase with age (Supplementary Table 2 given at the end of this article, Supplementary Figs 4 and 5 given at the end of this article). As evident in the data presented in Table 2 women present at a younger age than men. The SIR for women reaches its peak at the age of 35–39 years, but at 70–74 years for men (Supplementary Table 1 and Supplementary Fig. 6 given at the end of this article given at the end of this article).

Figure 1

Age at diagnosis. Age at diagnosis for all four tumour subtypes. Non-functioning pituitary adenomas (NFPAs) are diagnosed at a significantly higher age than prolactinomas ($P < 0.001$).

Non-functioning pituitary adenoma

NFPAs were most frequently diagnosed over the whole period (43.1%) but had the second highest prevalence rate (41.32/100 000) and SIR (2.2/100 000 per year for women vs 2.6/100 000 per year for men) after prolactinomas. There was an insignificant total male predominance (51.2% vs 48.8%). For the final time period the SIR for men was higher than for women but the difference did not reach statistical significance. Men presented at a significantly higher age than women (median age: 61 vs 53 for women; $P < 0.05$) and more had a macroadenoma (85.6% vs 62.6%; $P < 0.05$).

Prolactinoma

Prolactinomas were the second most commonly diagnosed subtype (39.9%) throughout the study period. Their final prevalence was the highest (54.37/100 000) as was their final SIR for women (3.6/100 000 per year), which is significantly higher than that for men (1.4/100 000 per year) ($P < 0.05$). Prolactinomas have had the highest SIR among women out of all subtypes since 1973 (Supplementary Table 1, see section on supplementary data given at the end of this article). The median age at diagnosis was 35 years and was significantly lower for women (median age: 32 vs 47 for males; $P < 0.001$). The majority of women had a microadenoma (72.3%) compared with 34% of men ($P < 0.001$).

Acromegaly

Acromegaly was the third most common diagnosis (11.3%). Final prevalence was 13.67/100 000 and SIR 0.8/100 000 per year for men and 0.4/100 000 per year

for women. There was a male predominance with a statistically significant difference in final SIR ($P < 0.05$) and final prevalence rates (9.01/100 000 for men vs 4.66/100 000 for women; $P < 0.05$). The median age at diagnosis was 45 years and did not differ significantly between the sexes. A significant majority among both sexes presented with a macroadenoma (62.5% for men and 71.4% for women).

Cushing's disease

Cushing's disease was the least common diagnosis, representing only 5.7% of the total number. Final prevalence reached 6.21/100 000, with a significant female predominance (5.28/100 000 vs 0.93/100 000 for men; $P < 0.05$). The SIR for men remained low throughout the period, peaking at 0.3/100 000/year between 1983 and 1992 but rose to 0.5/100 000/year for women within the final period. The majority of women had a microadenoma (70%), but because of limited information about size and characteristics on male patients diagnosed before 1990, further statistical analysis is impossible. The median age at diagnosis was 42, with no significant difference between the sexes.

Discussion

This is the first nationwide population-based study to establish the prevalence and incidence of PAs in a well-defined population over an extended period of time. Knowledge of the exact prevalence and current incidence of PAs is important to realise their true disease burden and

Figure 2

Changes in prevalence over time. Changes in prevalence rates for clinically significant pituitary tumours during 1972–2012 showing a clear rise since around 1990, mainly explained by the rising prevalence of prolactinomas and NFPAs.

Figure 3

Standardized incidence rates (SIR) for pituitary adenomas in Iceland during 1955–2012. (A) Total SIR for men and women. (B) SIR for each pituitary adenoma subtype during 1955–2012 for women. (C) SIR for each pituitary adenoma subtype during 1955–2012 for men. NFWA = non-functioning pituitary adenoma.

associated costs. This has long been a matter of significant debate, and studies through time have shown somewhat discordant results. Over 90 years ago, Costello conducted the first dedicated epidemiological study and found a prevalence of PAs of 22.5% at autopsy on asymptomatic subjects (17). A more recent systematic review of seven autopsy series found an overall prevalence of 14.4% (18). With the development and increased availability of pituitary imaging modalities, identification of PAs has become easier. The exact implication of this development is challenging to ascertain, but a review of available studies found a mean prevalence of 22.3%. In this same review by Ezzat *et al.* (18) a combined analysis including both

radiological and autopsy data yielded a final prevalence of unsuspected PAs of 16.7%.

Data from large databases such as cancer registries both in Europe and the USA suggest that PAs constitute 5–20% of primary central nervous system tumours and are the most common type both by site and by histology in young adults (20–34 years of age) (19, 20, 21).

These studies therefore suggest that PAs are common in the general population but most of them have no obvious clinical impact. Few well-designed intensive epidemiological studies on clinically significant PAs have been conducted. Studies done in the 1990s in the UK and Italy showed a prevalence of less than 300/million (22, 23). These retrospective studies done at tertiary referral centres are difficult to interpret because of the inability to define precise catchment areas and referral practices, and they do not represent a geographically defined population. In 2006 Daly *et al.* (6) conducted a cross-sectional study of PAs within the Liège province of Belgium, including a population of 71 972. They found a mean prevalence of 94 cases per 100 000. Prolactinomas were most frequent (66.2%); 14.7% of patients had NFWAs, 13.2% had acromegaly, and 5.9% had Cushing's disease (6). A more recent cross-sectional community-based study in Oxfordshire in the UK showed a similar prevalence of 77.6/100 000 inhabitants (7). A population-based study in Malta found an overall prevalence rate of 75.7/100 000 inhabitants in 2011, and an SIR of 4.27/100 000/year (8) based on a population of around 400 000 inhabitants and estimating SIR between 2000 and 2011. A previous Finnish study had found an overall SIR of 4.0/100 000 per year (10).

Our total prevalence rate of 115.57/100 000 is higher than that of any previous study. It is similar, but higher, than that reported by Daly *et al.* (94/100 000) (6), and even higher than that reported by Fernandez *et al.* (77.6/100 000) (7) and Gruppeta *et al.* (75.7/100 000) (8). Our final SIR of 5.8/100 000 per year is also higher than that previously reported in Malta (4.27/100 000 per year) (8) and by Raappana *et al.* (10) in Finland (3.98/100 000 per year). Possible reasons for these higher rates might include easier access to diagnostic facilities and medical staff in Iceland with more frequent imaging and earlier diagnosis, or possibly a trend related to these specific populations, such as genetics or environmental factors.

Our study does confirm the overall trends noted in the most recent studies, with rising prevalence rates and SIRs along with an increasing predominance of NFWAs. It is interesting to note that the prevalence in Iceland is now nearing half that of other much more recognized conditions, such as type 1 diabetes mellitus.

Our rank of subtype prevalence is the same as in all previous population-based studies – prolactinomas > NFPA > acromegaly > Cushing's disease – although their exact prevalence and incidence varies somewhat from previous studies. We found 47% of adenomas to be prolactinomas in 2012. This is very similar to that reported by Gruppettea *et al.* (46.2%) (8) but lower than that found by Daly *et al.* (66%) (6) and Fernandez *et al.* (57%) (7). We found 36% to be NFPA, which again is almost identical to that described in Malta, but higher than that in Belgium and the UK (6, 7, 8). The main trend observed is increased prevalence and incidence of NFPAs, with relative reduction in other subtypes compared with older studies. This may partly be related to the increased use of imaging facilities with an improved resolution and increased number of incidentalomas of which the majority are NFPAs. This, however, does not explain this trend fully (Supplementary Fig. 4, see section on supplementary data given at the end of this article). This may also be related to more accurate diagnoses, including that of NFPA with modest hyperprolactinaemia related to other causes possibly previously diagnosed as a prolactinoma. NFPAs are the most frequently diagnosed adenomas overall, but prolactinomas are the most prevalent at the end of the period. This may be related to the younger age at diagnosis for prolactinomas and possibly the high age at diagnosis and related mortality for patients diagnosed with NFPA. Although the current prevalence data may be the most obvious measure of disease burden, we believe the total number of tumours diagnosed reflects different but important aspects of disease burden. It is therefore important to present both types of data for comparison. Patients with prolactinomas are, for example, younger at diagnosis, resulting in higher cumulative prevalence, often requiring relatively simple treatment with dopamine agonists for a defined period of time. Patients with NFPAs are older, have more co-morbidities, and more often require surgery and more complex follow-up requiring more resources.

Our prevalence rate for acromegaly of 13.67/100 000 is similar to that reported by Gruppettea *et al.* (12.45/100 000) (8) but higher than that reported in the UK and Belgium (6, 7). The SIR reported in Iceland for the period of 2003–2012 (0.8/100 000 per year for men and 0.4/100 000 per year for women) is higher than that reported in both Malta and Finland (8, 10).

We found the prevalence of Cushing's disease to be higher than that found by Fernandez *et al.* and Gruppettea *et al.* (6.21/100 000 vs 1.2/100 000 and 2.2/100 000 respectively) (7, 8) but more similar to that reported by Daly *et al.* (6). Cushing's disease is a very rare condition

and much larger sample sizes are needed to fully assess the significance of these differences. We found a strong female predominance, which is similar to previous population-based studies.

In our study, the majority of adenomas were macroadenomas, and their final prevalence was higher than all other recent population-based studies but may again be related to the increasing prevalence of NFPAs and the increasing age of the general population, NFPA having a higher median age at diagnosis than other adenomas.

As noted in all previous studies, women present at a younger age with a higher proportion of microadenomas. In our study, the peak SIR for women is between the ages of 30 and 39 years, which corresponds well with previous studies reporting SIR. This tendency is probably related to the earlier presentation of women of childbearing age with hyperprolactinaemia due to menstrual irregularities and infertility than men with the corresponding symptoms of loss of libido, impotence, and general fatigue. This may of course be explained by a higher incidence of prolactinomas in this cohort, but it is important to note that NFPAs with modest prolactin rise can present with similar symptoms (24, 25). The peak SIR for the whole cohort is for men between the ages of 70 and 74 years (Supplementary Fig. 6, see section on supplementary data given at the end of this article), which differs from previous studies (8, 10), but may again relate to the increased incidence of NFPAs and advancing age of the population.

As previously described, this study includes 14 patients with negative imaging who fulfilled other diagnostic criteria for prolactinomas. This does differ from some previous studies. Excluding these patients, the total final prevalence for PAs falls to 111.22/100 000 and 50.02/100 000 for prolactinomas specifically. The study also includes four patients with Cushing's disease and three patients with acromegaly with negative imaging, who also fulfilled clinical and biochemical criteria and responded to treatment.

The median age at diagnosis in our study was 44 years, which is higher than in any other recent study. Gruppettea *et al.* found a median age of 39 years (8), Daly *et al.* 40.3 years (6), Fernandez *et al.* 37 years (7), and Raappana *et al.* 40 years (10). The age distribution is similar, however, with men and NFPAs presenting at an older age. Although the age range is wide (4–94 years), this does represent a relatively young economically productive population, which does stress the importance of the appropriate use of resources in their management.

A recent study using incidence data from 49 population-based state cancer registries in 2004–2009 in the

USA showed a significant rise in SIR during this period, as well as a significantly higher SIR in blacks (26). Iceland has a homogenous, well-defined population almost exclusively of white descent. This may be important when comparing our findings to other populations.

This study includes every PA diagnosed or registered in the total population of Iceland during the study period using all available diagnostic modalities. This approach differs somewhat from previous studies. Between the years 1958 and 1993, seven cases were registered in the Icelandic Cancer Register as having been found at autopsy (Supplementary Table 3, see section on supplementary data given at the end of this article). These are not included in the prevalence data but are included in the total number of cases. Their inclusion does not significantly affect SIRs calculated for any adenoma types since 1973. All seven adenomas are classified as NFPAs. Despite their exclusion, NFPAs remain the most commonly diagnosed adenomas in total (41.6%).

The rising incidence and prevalence of PAs have often been thought to be related to the increased use of imaging and increased incidence of incidentally discovered adenomas of uncertain significance. In our study, the vast majority of patients were symptomatic with only 16.1% of all adenomas being true incidental findings. Of these, seven were discovered at autopsy, so only 69 adenomas were diagnosed incidentally on imaging since 1955. The final prevalence of incidentally discovered adenomas was 15.89/100 000, slightly higher than that of acromegaly. It must be kept in mind that symptoms related to pituitary dysfunction can be very diffuse and non-specific, and they should therefore be included in the differential diagnosis of a variety of symptoms. The incidence data supports this by showing a modest rise in SIR for incidentalomas over the last 20 years but not nearly steep enough to explain the overall rise in SIR and prevalence rates (Supplementary Fig. 4, see section on supplementary data given at the end of this article).

The increasing availability of imaging modalities in Iceland is well documented. Prior to the introduction of the first CT scanners in 1981, imaging was done with standard X-ray. The first 0.5T MRI scanner arrived in 1992 followed by a 1.0T scanner in 1994 and a 1.5T scanner in 2004. Although it is impossible to be certain of a causal relationship, this corresponds well to the initial rise in frequency, especially for prolactinomas and NFPAs following the introduction of MRI (Supplementary Fig. 3, see section on supplementary data given at the end of this article). As most are symptomatic, this probably relates to a more accurate diagnosis using the appropriate

investigational tools rather than simple chance findings because of more frequent high definition imaging.

The limitations of this study include it being a retrospective observational exercise. Despite this, we are confident the cohort identified in this intensive case finding procedure is complete, as access was gained to all investigational and treatment facilities in Iceland. Unlike other recently published studies, we have included all incidentally discovered adenomas, which may explain the rising predominance of NFPAs. Incidentally discovered adenomas do require follow-up, treatment, and resources. In our cohort there was no significant difference in the proportion of patients needing surgery depending on presentation (symptomatic 30.2% vs incidental 27.6%). Characteristics of both groups are presented in Table 2. There is a possibility that patients with modest hyperprolactinaemia followed up by general practitioners or other specialist may have been missed, but these would not have had any imaging or any contacts at secondary or tertiary care. Their inclusion in the study would therefore, in any case, have been debatable.

The accurate clinical diagnosis and subclassification of PAs can be challenging. All clinical information and investigative results for all cases were scrutinised by a consultant endocrinologists using objective measures and internationally recognised guidelines and consensus statements where possible. Most patients had been followed and had contact with a number of specialists over an extended period of time, confirming their diagnosis. The data available on patients diagnosed prior to modern research facilities and the implementation of guidelines and consensus statements is in many ways limited, and diagnoses are not as firm. All available data was examined and upmost care taken to review every diagnosis using modern approaches. This applies to a small minority of our total cohort, and we believe we have made the most of the data available.

Conclusion

In this nationwide epidemiological study on PAs spanning almost six decades, we have confirmed their rising prevalence rates and standardized incidence rates. Compared with other recent studies, we did, however, find higher overall prevalence rates and incidences rates, which are not explained by incidental findings. There is a chronological relationship with the introduction of imaging modalities, but the vast majority of patients are symptomatic having appropriate investigations for their symptoms. Higher prevalence and incidence rates

underline the importance of increased awareness and education of all health care providers along with the appropriate allocation of resources.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-15-0189>.

Declaration of Interest

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

Funding

The authors received no external funding for this project.

Author contribution statement

All authors contributed sufficiently in the work to take public responsibility for its content. T T Agustsson, J G Jonasson, V Steinhorsdottir, G Sigurdsson, A V Thorsson, P V Carroll, M Korbonits, and R Benediktsson were involved in the study design. T T Agustsson and T Baldvinsdottir were involved in data collection. T T Agustsson, R Benediktsson, J G Jonasson, E Olafsdottir, P V Carroll, and M Korbonits were involved in data interpretation. T T Agustsson and E Olafsdottir were involved in statistical analysis. T T Agustsson drafted the manuscript. T T Agustsson, J G Jonasson, R Benediktsson, P V Carroll, and M Korbonits were involved in reviewing and improving the manuscript. Valgerður Steinþórsdóttir is affiliated with deCODE Genetics. Her contribution to this epidemiological study involves contribution to the study design and supervision through her role as a PhD supervisor in collaboration with the University of Iceland.

Acknowledgements

The authors would like to express our sincere gratitude to all clinicians who provided information and assisted in the data gathering, including Helga Augusta Sigurjonsdottir, Arna Gudmundsdottir, Gunnar Valtýsson, Bolli Thorsson, and Ari J Johannesson. They would also like to thank all other members of the staff at Landspítali, Domus Medica, and the Hospital in Akureyri who contributed to the study.

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Received 17 February 2015

Revised version received 15 August 2015

Accepted 21 August 2015