Incidence of Pituitary Adenomas in Northern Finland in 1992–2007

Antti Raappana, John Koivukangas, Tapani Ebeling, and Tapio Pirilä

Departments of Otorhinolaryngology (A.R., T.P.), Neurosurgery (J.K.), and Medicine (T.E.), Institute of Clinical Medicine, University of Oulu, FIN-90014 Oulu, Finland

Context: Data on the incidence of pituitary adenomas (PAs) are scant and outdated. A population-based regional cohort with thorough case identification was used to evaluate the incidence of clinically detected PAs in the era of magnetic resonance imaging.

Objective: The objective of the study was to describe the age- and sex-specific incidence of all PA subgroups, with data on incidentally found PAs, pituitary apoplexies, and time trends.

Design, Settings, and Patients: This was a retrospective descriptive analysis of PA patients diagnosed during 1992–2007 in Northern Finland (NFi).

Main Outcome Measure: World Health Organization 2000-standardized incidence rates (SIRs) of PAs per 100,000 were measured.

Results and Conclusion: The final cohort consisted of 355 PAs. The incidence rates of the Oulu University Hospital regional district were used as a reference to assess the applicability of our case finding over the rest of NFi. Incidence rates of all PA subgroups except microprolactinomas were statistically equal between these areas; thus, all presented SIRs are based on the NFi's cohort except Oulu University Hospital regional district-based prolactinomas and PAs overall. Overall SIR of PAs was higher (4.0 per 100,000) than in previous reports. Prolactinomas had the highest SIR: 2.2 per 100,000, followed by clinically nonfunctioning PAs (1.0) and GH-secreting (0.34), ACTH-secreting (0.17), and TSH-secreting (0.03) PAs. The gender-specific SIR was 2.2 per 100,000 in males and 5.9 per 100,000 in females. Pituitary apoplexy occurred as a presenting symptom in 11% of clinically nonfunctioning PA patients. The SIR of incidentally discovered PAs increased significantly from 1992–1999 to 2000–2007 (0.59 to 1.6, respectively; $P < 0.01$), which accounted for the perceived increasing trend in the overall SIR of PAs (3.8 to 4.2; $P > 0.05$). **(*J Clin Endocrinol Metab* 95: 4268–4275, 2010)**

Pituitary adenomas (PAs) are relatively common benign neoplasms of adenohypophyseal cells. As a results of the wide use of neuroradiological imaging, asymptomatic, incidentally detected PAs (incidentalomas) are becoming increasingly common (1, 2). In a recent review of autopsy and magnetic resonance imaging (MRI) studies, the overall estimated prevalence of PAs was 16.7% (3). Less commonly PAs are clinically relevant, causing symptoms by either secreting hormones (*e.g.* Cushing's syndrome, acromegaly) or mass effect (*e.g.* hypopituitarism, optic nerve compression). Although the primary treatment for prolactinomas is medical, surgery is currently the first treatment option for other types of PAs and as much as 25% of all intracranial tumor surgery is carried out for PAs (4).

Very few population-based epidemiological studies of PAs have been performed (5). Most published data about the epidemiology of different types of PAs are from single tertiary center surgical series (6), cancer registries (7), or autopsy reports (8, 9), which all represent biased popula-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2010-0537 Received March 5, 2010. Accepted May 18, 2010.
First Published Online June 9, 2010

Abbreviations: CI, Confidence interval; CIR, crude incidence rate; F/M, female to male; HCR, health care resource; MRI, magnetic resonance imaging; NF, nonfunctioning; NFi, Northern Finland; OUH, Oulu University Hospital; OUHRD, regional district of OUH; PA, pituitary adenoma; PRL, prolactin; SIR, standardized incidence rate.

tions, thus hindering reliable PA incidence or prevalence estimation. Just recently some well-designed PA prevalence studies have been published (10–12). However, PA incidences cannot be estimated from these cross-sectional studies, and published prevalence figures on PAs do not completely describe the health care resource (HCR) burden of the disease because many definitively cured PA patients are included. Thus, little is known about the true overall and hormonal subgroup incidences of PA, and recent incidence figures on PAs are needed to complement published prevalence data to estimate current and future HCR requirements of PAs.

Finland provides an exceptional opportunity to explore the incidence of PAs because all patients within a health care district are referred to their respective, predetermined centers, and public health services minimize the effect of socioeconomic factors by offering similar HCR access to all Finnish citizens. In Northern Finland (NFi), according to well-established practice, the great majority of suspected or diagnosed pituitary tumor patients (or the medical data and radiological images of the patient) is referred to Oulu University Hospital (OUH). This is the prevailing practice in all PA groups in which consideration for surgical treatment is the primary issue (*i.e.* practically all PAs except smaller prolactinomas) because all pituitary tumor operations in NFi are carried out at OUH. Thus, the PA patients of OUH form a geographical cohort concordant with that of NFi with the possible exception of some smaller prolactinomas.

The main purpose of this study was to describe the overall and subgroup incidences and patient demographics of clinically relevant PAs. In addition, we wanted to describe the proportion of incidentally found PAs, the incidence of pituitary apoplexy, the malignant transformation rate of benign PA, and time trends in PA incidence.

Materials and Methods

The study area comprises the four northernmost provinces of Finland (Fig. 1). To maintain uniformity of diagnostic criteria for the PAs throughout the study period, the years 1992–2007 were selected due to the availability of 1.5T MRI scanners. Data on the population at risk (5 yr age group and sex) by calendar year were obtained from Statistics Finland. During the study period, the annual (midyear) number of inhabitants in the area varied from 722,000 to 733,000. To evaluate the applicability of our case finding over the whole of NFi, the incidence rates of the regional district of OUH (OUHRD) were used as a reference for the rest of the NFi. OUHRD's population varied from 222,000 to 265,000 during the study period.

To collect patients with PAs as extensively as possible, a wide range of diagnosis numbers was selected (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org) in addition to conclusive ones (certain PA column in Supplemental Table 1) in searching the diagnosis, operation, and outpatient visit registries of OUH. In addition, the operation registry was searched using transsphenoidal operation codes. All new histologically confirmed PAs were included. Furthermore, all new clinically diagnosed patients with PA in which the diagnosis was reached by consensus by our sellar board (at least one senior endocrinologist, one neuroradiologist, and one pituitary surgeon) were included. Moreover, the cases that were not evaluated in the sellar board (the minority in which there was no surgical consideration; according to our treatment policy mostly smaller prolactinomas) were included only if the reevaluation of the patient's clinical follow-up data with laboratory results and imaging studies showed that the perceived lesion in the pituitary gland was a true PA. Tumors in the pituitary stalk, craniopharyngiomas, metastases, and other nonadenomatous sellar lesions and inflammatory processes in the sella were excluded.

FIG. 1. The geographical study area of the cohort of PA patients between 1992 and 2007 (*dark gray*) comprises geographically half of Finland's area and 14% of its population. The *hatched area* defines the OUHRD, inhabited by 5% of Finland's population.

To simplify the illustrations, multihormonally active PAs were classified into the group of the least common hormone [TSH < ACTH < GH < prolactin (PRL)] secreted by these PAs. All clinically nonfunctioning adenomas were classified as nonfunctioning (NF), regardless of their known histology (*e.g.* gonadotropinoma or null cell adenoma). PAs with a maximum diameter 10 mm or greater were classified as macroadenomas, smaller ones as microadenomas. The minimum diameter for a NF adenoma was 3 mm. This lower limit was not used in hormonally active PAs, but the PA had to be histo-

logically verified if it was not unarguably visible in the imaging studies.

Whether the discovery of the PA was incidental (*i.e.* imaging ordered without clinician's suspicion for pituitary pathology) was determined from the medical records of the included patients. In a few unclear cases, the patient's follow-up data were used to judge whether there was causality between the PA found and the patient's symptom (*e.g.* headache).

Pituitary apoplexy was defined as a sudden onset of symptoms such as severe headache, nausea, vomiting, vision loss, cranial nerve palsies, and altered consciousness with radiological evidence of hemorrhagic infarction of the PA (13).

We assumed that the incidence of PAs followed a Poisson distribution. The crude incidence figures were standardized to the World Health Organization 2000 standard population (14) using the direct method, and all the presented incidence rates are standardized incidence rates (SIRs) unless otherwise stated. All presented rates are per 100,000 unless otherwise stated. Differences between incidence rates were compared by calculating the 95% confidence interval (CI) for the rate differences. Continuous variables are presented as median and interquartile range, and differences in the distributions of independent samples were determined using the Mann-Whitney *U* test. The 95% CIs for categorical variables were determined based on normal approximation if n and n-x were greater than 5; otherwise, Wilson's method was used. Associations between categorical variables were analyzed using contingency tables and Fisher's exact test. A two-sided $P < 0.05$ was considered statistically significant. CIs and interquartile ranges presented in Table 1 are not replicated in the text. Mann-Whitney *U* and Fisher's exact test were carried out with PASW Statistics 18.0 for OsX software (SPSS Inc., Chicago, IL).

Results

In our primary registry search, 1666 patients were identified, of which 355 matched our inclusion criteria. In a simulated registry search using only the certain PA codes (Supplemental Table 1), the respective figures would have been 285 of 506 patients. At the same time, relying on the certain diagnoses in the registries, 70 of 355 (20%) of all PAs would not have been found and 221 cases with a wrong certain diagnosis code would have been included if the present final PA material were used as a gold standard. Thus, the certain-code search gave 80% (285 of 355) sensitivity and 56% (285 of 506) positive predictive value.

The OUHRD and the rest of NFi formed populations of 3.9 million and 7.8 million person-years at risk, respectively. Crude incidence rates (CIRs) for nonfunctioning or ACTH-, GH-, or TSH-secreting PAs did not statistically differ between these populations, but prolactinomas had a higher CIR in the OUHRD (2.2 *vs.* 0.71; $P < 0.01$). This difference was caused by underrepresentation of microprolactiomas in the rest of NFi because the CIR of macroprolactinomas, and more importantly PAs overall when prolactinomas were excluded, did not differ between these populations. Therefore, data of prolactinomas and PAs overall (because the PA overall figures include the data on prolactinomas) are presented based on the OUHRD cohort, whereas data of all other PA subgroups are based on whole NFi cohort.

The median follow-up time on the date of data collection was 7.5 yr (3.5–12.5). Eight PAs showed explicit clinical secretion or immunohistochemical staining positivity for more than one pituitary hormone: five GH+PRL, one ACTH+GH, one TSH+PRL, and one ACTH+GH+PRL. Six patients had multiple endocrine neoplasia type 1 syndrome (of these, all six secreted PRL, one also secreted TSH, four had macroadenomas, and five were females).

Overall age- and gender-related incidence of PAs

Detailed overall PA incidence figures in the OUHRD (n = 164) with their CIs are presented in Table 1. The overall age- and sex-specific incidences are presented in Fig. 2A. The overall PA SIR was 4.0, and females had higher SIR than males (5.9 and 2.2, respectively). Females were younger than males (median age 36 *vs.* 50 yr; $P = 0.006$). The incidence of PA increased with age in males (Fig. 2A), whereas the prolactinomas in fertile-aged women caused a twin-peaked incidence-age profile in females. Overall both-sex PA incidence reached its maximum of 6.7 in the age group of 30–39 yr.

PRL-secreting adenomas

Prolactinomas (n = 84 in the OUHRD) had the highest SIR of 2.2, and contributed 51% of all PAs. There was a considerable peak in the incidence in women of child-bearing age (Fig. 2B), and in the third decade of life, the female to male (F/M) incidence ratio was 6.3. Males had a constant increase in the incidence of prolactinomas throughout their adult life span, and males constituted the majority (88%) of those patients with prolactinomas diagnosed after the age of 50 yr. Males had more macroprolactinomas (75% of males' prolactinomas) than did women (16%; $P < 0.001$).

Clinically NF adenomas

Clinically NF adenomas (n = 154 in NFi, n = 59 in the OUHRD) contributed 37% of all PAs, and the overall SIR was 1.02. Clinically NF adenomas had a unique tendency to increase in frequency with older age, especially in men (Fig. 2C). Of clinically NF adenomas, 82% were macroadenomas.

GH-secreting adenomas

GH-secreting PAs (n = 40 in NFi, n = 14 in the OUHRD) contributed 8.5% of all PAs. The SIR was 0.34. Five (13%) also secreted PRL. Only the GH sub-

TABLE 1. Study patients grouped by hormonal subgroups in order of decreasing incidence

	PRL			NF			GH			ACTH			TSH			PAs overall		
Area of which data forms the group	OUHRD			Northern Finland			Northern Finland			Northern Finland			Northern Finland			OUHRD		
Proportion of all adenomas (95% CI)[a]	0.51 (0.44–0.59)			0.36 (0.29–0.44)			0.09 (0.05–0.14)			0.03 (0.01–0.07)			0.01 (0–0.04)			1		
Number of cases (OUHRD, n)	84 (84)			154 (59)			40 (14)			19 (5)			3 (2)			164 (164)		
Age range (yr)	13–72			19–85			12–69			11–69			21–30			13–81		
F/M ratio (95% CI)	4.3 (2.48–7.28)			1.2 (0.87–1.65)			0.6 (0.32–1.13)			2.8 (1.05–7.47)			2.0 (0.26–15.3)			2.5 (1.78–3.49)		
	n	**Rate**	**95% CI**	**n**	**Rate**	**95% CI**	**n**	**Rate**	**95% CI**	**n**	**Rate**	**95% CI**	**n**	**Rate**	**95% CI**	**n**	**Rate**	**95% CI**
Standardized rate (WHO 2000)/100,000	84	2.16	1.7–2.63	154	1.02	0.86–1.19	40	0.34	0.23–0.44	19	0.17	0.09–0.25	3	0.03	0.00–0.07	164	3.98	3.37–4.6
Females	68	3.71	2.82–4.59	84	1.15	0.89–1.41	15	0.27	0.13–0.41	14	0.26	0.12–0.40	2	0.05	0.00–0.11	117	5.86	4.78–6.94
Males	16	0.76	0.39–1.13	70	0.93	0.71–1.15	25	0.4	0.24–0.56	5	0.1	0.01–0.18	1	0.02	0.00–0.05	47	2.22	1.59–2.86
	n	**Median**	**Interq.r.**	**n**	**Median**	**Interq.r.**	**n**	**Median**	**Interq.r.**	**n**	**Median**	**Interq.r.**	**n**	**Median**	**Interq.r.**	**n**	**Median**	**Interq.r.**
Median age at diagnosis (yr)	84	32.5	25.3–41.8	154	60	49–70	40	40.5	30.5–47.8	19	28	16–45	3	24	na	155	40	27.3–55
Females (yr)	68	32	25–39	84	58.5	45–69	15	38	27–54	14	32	20.8–50	2	22.5	na	117	36	27–49.5
Males (yr)	16	47.5	32.3–61.5	70	62	54.8–71	25	41	32–45.5	5	22	13.5–33.5	1	30	na	47	50	32–62
	n	**Proportion**	**95% CI**	**n**	**Proportion**	**95% CI**	**n**	**Proportion**	**95% CI**	**n**	**Proportion**	**95% CI**	**n**	**Proportion**	**95% CI**	**n**	**Proportion**	**95% CI**
Secreted other hormones (see legend)	2	0.03	0.01–0.09	na	na	na	7	0.18	0.06–0.29	2	0.11	0.03–0.31	1	0.33	0.06–0.79	2	0.01	0–0.04
Macroadenoma proportion within group	23	0.27	0.19–0.38	126	0.82	0.75–0.87	31	0.78	0.62–0.88	7	0.37	0.19–0.59	3	1	0.44–1	76	0.46	0.39–0.54
Females	11	0.16	0.09–0.27	64	0.76	0.66–0.84	11	0.73	0.48–0.89	6	0.43	0.21–0.67	2	1	0.34–1	42	0.36	0.28–0.45
Males	12	0.75	0.51–0.9	62	0.89	0.79–0.94	20	0.8	0.61–0.91	1	0.2	0.04–0.62	1	1	0.21–1	34	0.72	0.58–0.83
Incidentalomas (both sexes)	7	0.7	0.4–0.89	53	0.68	0.57–0.77	4	1	0.51–1	na	na	na	na	na	na	29	0.57	0.43–0.69
Incidentaloma proportion within group	10	0.12	0.07–0.21	78	0.51	0.43–0.58	4	0.1	0.04–0.23	0	0	0–0.17	0	0	0–0.56	51	0.31	0.25–0.39
Females	2	0.03	0.01–0.1	44	0.52	0.42–0.63	3	0.2	0.07–0.45	0	0	0–0.22	0	0	0–0.66	31	0.26	0.19–0.35
Males	8	0.5	0.28–0.72	34	0.49	0.37–0.6	1	0.04	0.01–0.2	0	0	0–0.43	0	0	0–0.79	20	0.43	0.29–0.57
Pituitary apoplexy within group	1	0.01	0–0.06	17	0.11	0.07–0.17	0	0	0–0.09	2	0.11	0.03–0.31	0	0	0–0.56	6	0.04	0.02–0.08
As a presenting symptom	0	0	0–0.79	17	1	0.82–1	na	na	na	2	1	0.34–1	na	na	na	5	0.83	0.44–0.97
Clinical treatment																		
Pituitary surgery within group	14	0.17	0.1–0.26	91	0.59	0.51–0.67	38	0.95	0.83–0.99	18	0.95	0.75–0.99	3	1	0.44–1	63	0.38	0.31–0.46
Proportion of incidentalomas operated on	1	0.1	0.02–0.4	28	0.36	0.26–0.47	4	1	0.51–1	na	na	na	na	na	na	13	0.25	0.16–0.39
Revision surgery (of operated patients)	2	0.14	0.04–0.4	20	0.22	0.15–0.32	4	0.11	0.04–0.24	2	0.11	0.03–0.33	0	0	0–0.56	14	0.22	0.14–0.34

Prolactinoma (PRL) and PAs over all columns and the second row ([a]) are based on data from the OUHRD cohort; values in all other cells are based on the data of whole NFi cohort. This presentation approach was chosen because the study patients statistically presented the population of the whole of Northern Finland with the exception of the subgroup of microprolactinomas. Eight multihormone-secreting adenomas are grouped into the rarest (TSH < ACTH < GH < PRL) hormonal subgroup that they secrete. However, in the Secreted other hormones row, this classification is omitted (*e.g.* GH- and PRL-secreting adenomas are presented in both the GH and PRL columns). NF, Clinically nonfunctioning pituitary adenomas; interq.r., interquartile range; na, not applicable.

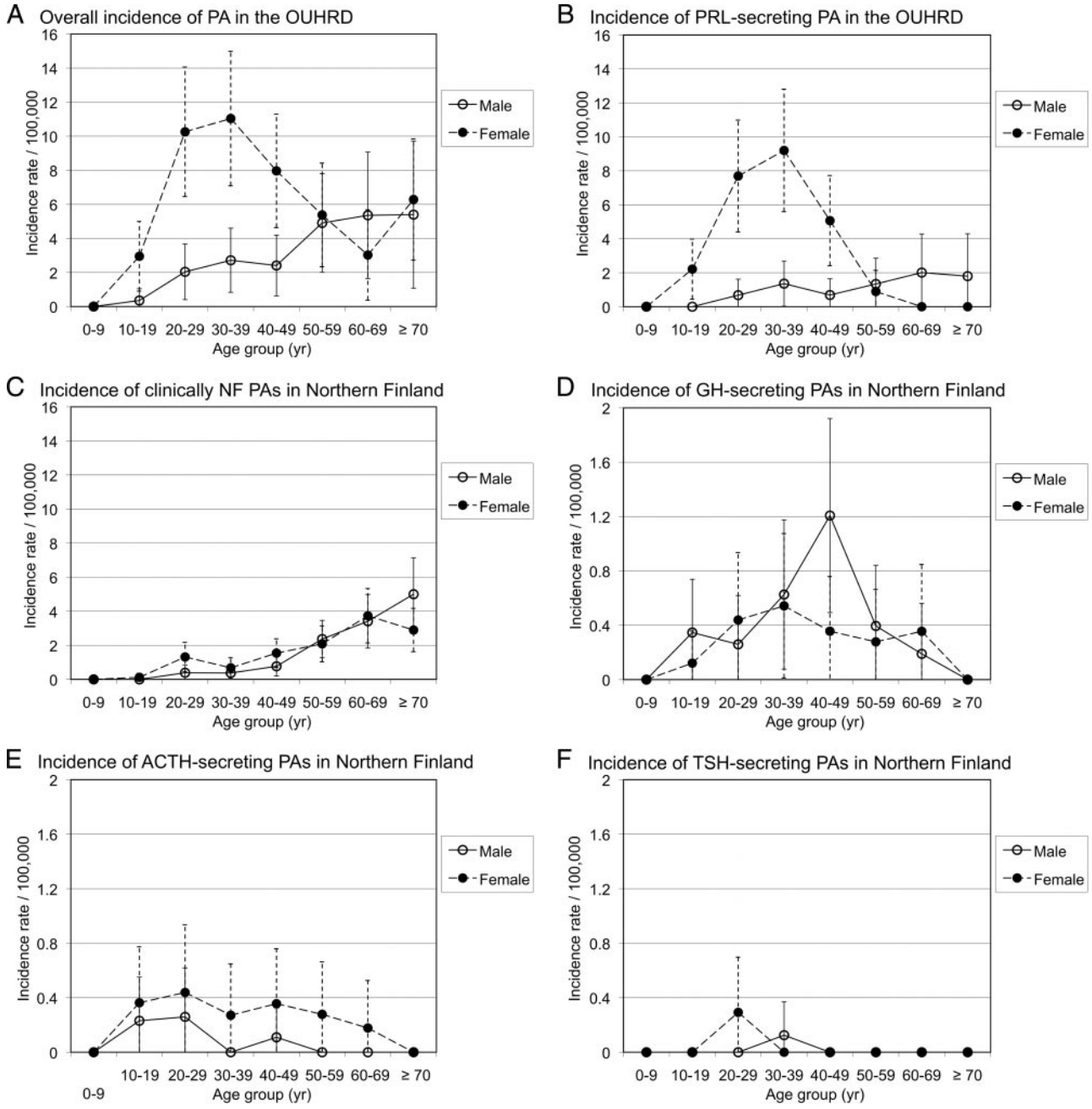

FIG. 2. Overall and subclass PA incidences per 100,000 person-years. Corresponding to Table 1, overall PA (A) and prolactinoma (B) incidences are based on the OUHRD, whereas the other groups (C–F) are based on the whole population of northern Finland. Note the different scales of the y-axes in A–C and D–F.

group showed a tendency for male predominance (F/M case ratio 0.6; $P = 0.11$). Males reached the peak incidence rate of 1.37 in the fifth decade of life (Fig. 2D). There were 78% macroadenomas.

ACTH-secreting adenomas

ACTH secretion was present in 3.0% (n = 19 in NFi, n = 5 in the OUHRD) of all PAs, and females had a preponderance (F/M case-ratio 2.8; $P = 0.04$) in this subgroup. The SIR was 0.17. In addition to ACTH, one PA also secreted GH and another also GH and PRL. The incidence peak took place in teenagers and young adults, and four of the study's seven PAs diagnosed under the age of 15 yr were ACTH secreting. Twelve of the ACTH-secreting PAs (63%) were microadenomas, and in five (26%) of these cases, the MRI finding was only suggestive or normal. However, each was confirmed histologically after surgery.

TSH-secreting adenomas

TSH-secreting PAs were rare (n = 3 in NFi, n = 2 in the OUHRD; 1.2%). The SIR was 0.032. All were macroad-

enomas occurring in young adults. One 25-yr-old female had multiple endocrine neoplasia type 1 syndrome, and her tumor also secreted PRL.

Occurrence, time trend, and clinical treatment of incidentalomas

Because incidentally found PAs are analyzed here as constituting a part of all PAs, only data for incidentalomas in the OUHRD cohort (n = 51) are presented. An incidentaloma was a totally unexpected finding in 31% (51 of 164) of the OUHRD patients; the imaging modality of a (suggestive) PA finding was MRI in 61%, computed tomography in 37%, and plain film x-ray in 2% of the incidentaloma patients. Incidentalomas tended to be found more often in males (43% of all males' PAs) than females (26%; $P = 0.06$). Of females' incidentalomas (n = 31), 84% were clinically nonfunctioning, 10% secreted GH, and 6% secreted PRL. Respective figures for 20 males were 60, 0, and 40%.

Whereas the incidence of clinically suspected PAs remained stable between 1992–1999 and 2000–2007 (n = 60 and n = 53, respectively), the incidence of incidentalomas tripled (n = 12 and n = 39, respectively; $P < 0.001$). This corresponded to the significant increase in SIR of incidentalomas between study halves (0.59 to 1.6; $P < 0.01$) and a statistically not significant increase in overall PA SIR (3.8 to 4.2; $P > 0.05$).

Hormonally active, incidentally found GH- and PRL-secreting adenomas were operated on as often as corresponding PAs found on the basis of their symptomologies. In addition, 28 of 78 incidentally found NF PAs (36%) were operated on because of subsequently developed or noticed mass-effect-related symptoms or growth tendency.

Apoplexy

Classical pituitary apoplexy with dramatic general symptoms was a rare occurrence (n = 20 in NFi; 0.17 episodes per 100,000 per year). It was the presenting symptom in 11% of both ACTH and clinically NF PAs but was not seen in other types of PA. However, one patient with a prolactinoma suffered an apoplectic event after 1 yr on dopamine agonist treatment. In the ACTH adenoma group, apoplexy occurred in the oldest patients with the largest adenomas.

Malignant transformation of PAs

There was one PA with a malignant transformation during the study period. Thus, the crude incidence of malignant PA after detection and treatment of the PA was one per 2715 person-years at risk; 0.09 per 1 million per year at risk when the whole study population is included. No primary pituitary carcinoma was detected.

Discussion

Epidemiological data form the cornerstone of health policy. The existing population-based incidence data on PAs are scant, and MRI- and autopsy-based series are discordant with tertiary centers' surgical series. Cross-sectional prevalence studies do not completely describe the HCR requirements in a clinical setting, and up-to-date incidence figures of PAs are needed to complement recent prevalence studies (10–12) for HCR planning. In addition, knowledge about local geographical PA incidence figures enables understanding of possible geographical epidemiological differences and changes in local and global incidence trends.

To our knowledge, the present study is the most extensive one carried out in the era of MRI that evaluates the incidence of clinically detected pituitary adenomas in a population-based cohort. Our thorough case identification seems to been successful in the OUHRD because these 164 new cases diagnosed among the population averaging 242,400 persons during the 16-yr period contribute to a prevalence of 68 per 100,000 at the end of the study period. Taking into account that a 16-yr period is a relatively short proportion of Finnish life expectancy and that PAs overall, in the era of present diagnostic and treatment modalities, should at most cause only a minor increase in mortality (7, 15, 16), the perceived prevalence of 68 would translate into a true prevalence higher than in recent prevalence studies by Fernandez *et al.* (10), 78 per 100,000; Daly *et al.* (11), 94 per 100,000; and Fontana and Gaillard (12), 81 per 100,000. Furthermore, although we did our case identification process only from the registries of OUH, we found equal CIRs in OUHRD and the rest of NFi for all but microprolactinoma PA groups, thus confirming our hypothesis that OUH-centered coordination of PA patients' treatment is the prevailing practice in Northern Finland, with the exception of only microprolactinomas. This exception is reasonable and shows that gynecologists and/or endocrinologists in the secondary level hospitals of Northern Finland treat some microprolactinomas without consulting OUH. Therefore, data on prolactinomas and hence overall PA group relations were analyzed based on the OUHRD population.

The incidences of diseases are commonly approximated based on hospital (17, 18) or national registry (7) databases. On the basis of histological confirmation the results would become more specific, but then only surgically treated patients would be included. If histological confirmation is not required, a significant number of suspected diseases would be included. The present results confirmed this hypothesis because the certain PA diagnosis search initially gave a low positive predictive value of

56% together with only a moderate sensitivity of 80%. With this approach, 99% of surgically treated patients would have been found, but 38% of conservatively treated patients would have been omitted.

The scarce data on age-specific incidence of PAs are from the pre-MRI era, especially those of PA subclasses. In a population-based study, Leibowitz *et al.* (19) observed the highest incidence in the 40- to 69-yr age group (two per 100,000/yr), followed by a decline in older ages, during 1960–1966 in Israel. In the small numbered study of Annegers *et al.* (20) in Minnesota in 1978, the investigators reported the incidence of PAs to be as high as 7.1 per 100,000/yr in women of child-bearing age, decreasing thereafter, in contrast to men whose PA incidence increased with age. The present results are concordant with those of Annegers *et al.*, with the highest incidence in fertile-aged females and an increase in incidence with age in males (Fig. 2A). However, in our more recent study with modern diagnostic abilities, there was a second peak in incidence in females after the age of 70 yr, and the overall SIR (4.0) was significantly higher than in these older studies.

Prolactinomas have been the most common PA subgroup in a surgical series (6), an autopsy report (8), and several clinical prevalence studies (10–12). Prolactinomas had the highest subgroup incidence in the present study, also. The presented 36% proportion of NF PAs is somewhat higher than in these previous reports (6, 8, 10–12), but this might be a sign of an existing trend in which the use of modern imaging technologies reveals continuously more incidental PAs, and most incidentalomas (75% in the present study) are clinically nonfunctioning. The present proportions of GH-, ACTH-, and TSH-secreting subgroups of all PAs are parallel with European prevalence studies (10–12) despite the described classification of the multihormonally active adenomas, which causes a bias toward the less common PA subgroups. However, interestingly, the described classification sounds reasonable because it highlights PAs with the more morbidity-causing hormone, perhaps with the exception of rare thyrotropinomas.

The most common PA subgroup in this study contributing half of all PAs was prolactinoma, of which 73% were microadenomas. Although surgery is not the first-line treatment option in prolactinomas, these tumors require a significant amount of HCR in the form of multiple follow-up visits, pituitary function tests, and MRI scans in addition to medical therapy and possible visual field testing. Furthermore, 17% of prolactinomas were operated on in this study. The management of other PA subgroups requires even greater resource use than for prolactinomas (11). Incidentally found PAs (31% in the present study) do not make an exception for the HCR consumption; before the indolent nature of an incidentally found PA can be confirmed, they can cause the very same HCR burden described for prolactinomas up to 20 yr (21), although the follow-up approach to incidentalomas may vary. Moreover, incidentalomas were often found to be causing undiagnosed hormonal hypersecretion (*e.g.* 10% of the study's acromegalics were found incidentally), unnoticed visual field defects, or hypopituitarism, and eventually 25% of the study's incidentalomas were operated on.

Malignant transformation of PAs is rare (22). We report only one malignant transformation in a PA population of 2715 person-years at risk and not a single primary pituitary carcinoma in a population of 11.6 million person-years at risk.

There has been debate about whether the real incidence of pituitary adenomas is increasing or whether improved diagnostic techniques and skills, increased awareness of pituitary diseases, or longer life expectancy have caused the phenomenon (7, 10). The present study clearly demonstrates that the increase in the incidence of PAs during this 16-yr study period was not caused by an increase in symptomatic PAs but rather by an increased incidence of incidentalomas in neuroradiological imaging. It is important to note, as discussed above, that incidentalomas do cause significant HCR burden. High HCR use in the setting of the much-increased incidence of PAs represents an important issue for calculating medical and research budgets, although confirmation in formal pharmacoeconomic studies is required (11).

There are some limitations in the present study. The study was executed retrospectively using data found in the OUH records. This caused definite underrepresentation of microprolactinomas when the whole of NFi is regarded, but this limitation was mainly overcome by analyzing data related to prolactinomas from the fairly large OUHRD cohort. A lack of uniform diagnostic criteria is another limitation but is compensated for by the described sophisticated case selection after the median 7.5-yr follow-up time.

Conclusion

In summary, the present study gives modern, reliable incidence rates of pituitary adenomas in a well-defined geographical area. In addition, the occurrence of incidentally found PAs is presented, and it is demonstrated that the increase in the incidence of PAs during the study period was caused by an increased incidence of incidentalomas. Our thorough case identification process gives good estimates of the true incidence of PAs in the era of modern diagnostic tools in a Western country, but whether there are true geographical variations in the epidemiology of PAs remains open.

Acknowledgments

Address all correspondence and requests for reprints to: Antti Raappana, M.D., Department of Otorhinolaryngology, Institute of Clinical Medicine, University of Oulu, P.O. Box 5000, FIN-90014 Oulu, Finland. E-mail: antti.raappana@oulu.fi.

Disclosure Summary: The authors have nothing to disclose.

References

1. **Sanno N, Oyama K, Tahara S, Teramoto A, Kato Y** 2003 A survey of pituitary incidentaloma in Japan. Eur J Endocrinol 149:123–127
2. **Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, Niessen WJ, Breteler MM, van der Lugt A** 2007 Incidental findings on brain MRI in the general population. N Engl J Med 357:1821–1828
3. **Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, McCutcheon IE** 2004 The prevalence of pituitary adenomas: a systematic review. Cancer 101:613–619
4. **Asa SL, Ezzat S** 2002 The pathogenesis of pituitary tumours. Nat Rev Cancer 2:836–849
5. **Daly AF, Tichomirowa MA, Beckers A** 2009 The epidemiology and genetics of pituitary adenomas. Best Pract Res Clin Endocrinol Metab 23:543–554
6. **Mindermann T, Wilson CB** 1994 Age-related and gender-related occurrence of pituitary adenomas. Clin Endocrinol (Oxf) 41:359–364
7. **Nilsson B, Gustavasson-Kadaka E, Bengtsson BA, Jonsson B** 2000 Pituitary adenomas in Sweden between 1958 and 1991: incidence, survival, and mortality. J Clin Endocrinol Metab 85:1420–1425
8. **Burrow GN, Wortzman G, Rewcastle NB, Holgate RC, Kovacs K** 1981 Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. N Engl J Med 304:156–158
9. **Teramoto A, Hirakawa K, Sanno N, Osamura Y** 1994 Incidental pituitary lesions in 1,000 unselected autopsy specimens. Radiology 193:161–164
10. **Fernandez A, Karavitaki N, Wass JA** 2010 Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol (Oxf) 72:377–382
11. **Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A** 2006 High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J Clin Endocrinol Metab 91:4769–4775
12. **Fontana E, Gaillard R** 2009 Epidemiology of pituitary adenoma: results of the first Swiss study. Rev Med Suisse 5:2172–2174
13. **Randeva HS, Schoebel J, Byrne J, Esiri M, Adams CB, Wass JA** 1999 Classical pituitary apoplexy: clinical features, management and outcome. Clin Endocrinol (Oxf) 51:181–188
14. **Ahmad OE, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M** 2000 Age standardization of rates: a new WHO standard. GPE discussion paper series 31. Geneva: World Health Organization
15. **Lindholm J, Juul S, Jørgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, Hagen C, Jørgensen J, Kosteljanetz M, Kristensen L, Laurberg P, Schmidt K, Weeke J** 2001 Incidence and late prognosis of Cushing's syndrome: a population-based study. J Clin Endocrinol Metab 86:117–123
16. **Kauppinen-Mäkelin R, Sane T, Reunanen A, Välimäki MJ, Niskanen L, Markkanen H, Löyttyniemi E, Ebeling T, Jaatinen P, Laine H, Nuutila P, Salmela P, Salmi J, Stenman UH, Viikari J, Voutilainen E** 2005 A nationwide survey of mortality in acromegaly. J Clin Endocrinol Metab 90:4081–4086
17. **Kuratsu J, Takeshima H, Ushio Y** 2001 Trends in the incidence of primary intracranial tumors in Kumamoto, Japan. Int J Clin Oncol 6:183–191
18. **Vrkljan M, Matovinović M, Marić A, Bekić M, Zah T, Resetić J, Vizner B, Pećina HI, Cerina V, Gnjidić Z** 2006 Incidence of pituitary tumors in the human population of Croatia. Coll Antropol 30:157–161
19. **Leibowitz U, Yablonski M, Alter M** 1971 Tumors of the nervous system. Incidence and population selectivity. J Chronic Dis 23:707–721
20. **Annegers JF, Coulam CB, Abboud CF, Laws Jr ER, Kurland LT** 1978 Pituitary adenoma in Olmsted County, Minnesota, 1935–1977. A report of an increasing incidence of diagnosis in women of childbearing age. Mayo Clin Proc 53:641–643
21. **Molitch ME** 2009 Pituitary tumours: pituitary incidentalomas. Best Pract Res Clin Endocrinol Metab 23:667–675
22. **Kars M, Roelfsema F, Romijn JA, Pereira AM** 2006 Malignant prolactinoma: case report and review of the literature. Eur J Endocrinol 155:523–534