Higher incidence of morbidity in women than men with non-functioning pituitary adenoma: a Swedish nationwide study

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Abstract

Objective: Increased mortality rates are found in women and young adults with non-functioning pituitary adenomas (NFPAs). This nationwide study aimed to investigate the burden of comorbidities in patients with NFPA and to examine whether gender influences the outcome.

Design: NFPA patients were identified and followed-up from National Registries in Sweden. It was a nationwide, population-based study.

Method: Standardised incidence ratios (SIRs) for comorbidities with 95% confidence intervals (CI). Comorbidities were analysed in all patients, both patients with and without hypopituitarism.

Results: Included in the analysis were 2795 patients (1502 men, 1293 women), diagnosed with NFPA between 1987 and 2011. Hypopituitarism was reported in 1500 patients (54%). Mean patient-years at risk per patient was 7 (range 0–25). Both men (SIR 2.2, 95% CI: 1.8–2.5; $P < 0.001$) and women (2.9, 2.4–3.6; $P < 0.001$) had a higher incidence of type 2 diabetes mellitus (T2DM) than the general population, with women having a higher incidence compared with men ($P = 0.02$). The incidence of myocardial infarction was increased in women (1.7, 1.3–2.1; $P < 0.001$), but not in men. Both men (1.3, 1.1–1.6; $P = 0.006$) and women (2.3; 1.9–2.8; $P < 0.001$) had an increased incidence of cerebral infarction, with women having a higher incidence than men ($P < 0.001$). The incidence of sepsis was increased for both genders. The incidence of fractures was increased in women (1.8, 1.5–1.8; $P < 0.001$), but not for men.

Conclusions: This nationwide study shows excessive morbidity due to T2DM, cerebral infarction and sepsis in all NFPA patients. Women had higher incidence of T2DM, myocardial infarction, cerebral infarction and fracture in comparison to both the general population and to men.

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Introduction

Patients with hypopituitarism have an increased mortality ratio, mainly due to respiratory, cardiovascular and cerebrovascular causes (1, 2, 3, 4, 5). The reason for the excessive mortality is currently not fully understood although some factors associated with increased risk have been identified. Patients diagnosed at young age have 2.7 times higher mortality compared with the general population (6). Women have also an increased risk of premature death compared with men as well as

patients with pituitary adenoma operated by transcranial surgery compared with those treated by transphenoidal surgery (3). Pituitary radiation therapy, untreated growth hormone deficiency and high glucocorticoid replacement doses may also implicate increased risk (2, 3, 7, 8, 9).

As almost all previous studies have investigated heterogeneous groups of patients with hypopituitarism of various aetiologies, the increased mortality may not solely be due to the hormone deficiencies but also to the

underlying disease itself, such as Cushing's disease or craniopharyngioma. In an attempt to bypass this potential bias, we have recently studied mortality in a large cohort of patients with a single aetiology, non-functioning pituitary adenomas (NFPAs) (6). Despite this approach, with a homogenous population, an increased mortality was observed, especially among women and patients diagnosed with NFPA before the age of 40 years. To date, there is no explanation for the worse prognosis in women and young patients.

The aim of this nationwide population study was to investigate the burden of cerebral infarctions, myocardial infarctions, type 2 diabetes mellitus, fractures and sepsis in patients with NFPA and to examine whether gender and age at diagnosis influence the outcome.

Subjects and methods

Study design

Patients with NFPA diagnosis were identified in The Swedish National Patient Registry (Patient Registry). The registry achieved national coverage in 1987 and contains information from every patient visit within the Swedish hospital system. An individual patient can be followed throughout life in the Swedish National Health registries using a unique Swedish personal identification number. The National Board of Health and Welfare secures high quality for the Patient Registry (10). To identify patients with NFPA diagnosis, we used a combination of identification criteria to ensure a high quality in the selection of the patients. The identification process has been previously described in detail in a study when mortality in the Swedish national cohort of patients with NFPA was studied (8). In short, patients should have been diagnosed with NFPA (International Classification of Diseases, 10th revision (ICD-10) code D35.2) either at a medical/endocrine care unit or at a neurological or neurosurgical care unit. This method of combined criteria for identification (both diagnostic codes and department codes) has previously been shown to achieve a high sensitivity and specificity when selecting patients with pituitary diseases in epidemiological research (11, 12). All patients with a diagnosis of a GH-, ACTH-, or TSH-secreting adenoma; prolactinoma; craniopharyngioma; pituitary cyst or a pinealoma were excluded before the inclusion criteria were applied to the registries. To further ensure a high quality, an internal validation of the selection criteria was performed by reviewing the NFPA diagnosis of patients originating from the Sahlgrenska

University Hospital's uptake area (17% of the total patient population) against patient records. The NFPA diagnosis was confirmed in 424 patients, which resulted in a positive predictive value of 91%. Other non-functioning pituitary tumours, mostly cystic pituitary tumours, were found in 4% of the patients. Only 1% of the patients had a lesion not affecting the sella region (6). In patients with cystic pituitary tumours, 11 out of 14 patients were women.

Patients with NFPA were identified in the Patient Registry from 1 January 1997 (when ICD-10 classification was implemented in Sweden) to 31 December 2011. The date of the NFPA diagnosis was also gathered from the Patient Registry. Patients that had deceased or emigrated before 1 January 1997 were not included in the cohort. The time at risk for the patients with NFPA started on the date of diagnosis (date of the first registered NFPA diagnosis). The start of the investigation period was 1 January 1987. The time at risk, in which patients were studied regarding morbidity, ended on the date of death or at the end of the study, 31 December 2011. Date of birth, gender, diagnoses of hypopituitarism and diabetes insipidus (DI) and radiotherapy were collected from the Patient Registry. The degree of hypopituitarism and its management were not available in the registry. Information regarding radiotherapy was obtained in patients diagnosed between 1 January 1997 and 31 December 2011 (during the ICD-10 classification period). Morbidity data for cerebral infarctions, myocardial infarctions, diabetes mellitus, fractures and sepsis were also collected from the Patient Registry and classified in accordance with the ICD classification (for ICD-codes, [Supplementary Material](#), see section on [supplementary data](#) given at the end of this article). Data on comorbidities in the general population were gathered and analysed in the same manner as for the patients.

Ethics

The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden, and by the National Board of Health and Welfare, Sweden.

Statistical analysis

Person-years at risk were calculated from study inclusion to death or end of study and stratified according to gender, 5-year age groups and 1-year calendar periods. The expected number of cases for each stratum was calculated using the general Swedish population as reference. The observed number of comorbidities among subjects with

NFPA was compared with those expected in the general population using standardised incidence ratios (SIRs). SIRs for each diagnosis were calculated depending on whether the patients received the specific diagnosis on a yearly basis with the exception of type 2 diabetes mellitus, which was analysed based on the first event only. Ninety-five percent confidence intervals (CIs) were calculated assuming a Poisson distribution of the observed numbers. Subgroup analyses for gender, age at diagnosis, hormonal deficiencies and radiotherapy were performed. If fewer than four events were observed, no estimate was made for SIR. SIRs for non-overlapping subgroups were compared with each other (13). No patients in the validated subgroup originating from the Sahlgrenska University Hospital's uptake area were lost to follow-up, e.g. due to emigration. IBM SPSS (version 21; SPSS) and STATA/SE (version 12.1; Statacorp) software were used for the statistical analyses.

Results

This nationwide study included 2795 unique patients with NFPA (1502 men and 1293 women; Table 1). The mean age at diagnosis was 58.4 ± 17 years and the mean person-years at risk per patient was 7.2 (range 0–25) years. The length of the person-years at risk per patient did not differ between men ($7.2 \text{ years} \pm 5.4$) and women ($7.2 \text{ years} \pm 5.2$). In total, 20 139 patient-years were included in the study.

Table 1 Characteristics of patients with non-functioning pituitary adenoma.

	Total (n = 2795)
Gender, n (%)	
Men	1502 (54)
Women	1293 (46)
Age at diagnosis, y, mean (range)	58.4 (1–97)
Men, mean $\pm$ s.d.	60.2 $\pm$ 15
Women, mean $\pm$ s.d.	56.2 $\pm$ 18
Mean patient-years at risk per patient, y (range)	7 (0–25)
Patient-years at risk in the study	20 139
Hormonal status, n (%)	
Patients with hypopituitarism	1500 (54)
Patients with diabetes insipidus	145 (5)
Patients without any hormonal deficiencies	1266 (45)
Patients diagnosed at or before 40 years of age, n (%)	423 (15)
Time of diagnosis, n (%)	
Patients diagnosed before 1 January 1997	322 (12)
Patients diagnosed between 1 January 1997 and 31 December 2011	2473 (88)
Radiotherapy of patients diagnosed between 1 January 1997 and 31 December 2011	104 (4)

The diagnoses of hypopituitarism and DI were recorded in 1500 patients (54%) and in 145 patients (5%) respectively. More men ($n=957$, 63%) than women ($n=572$, 44%) were diagnosed with hypopituitarism and/or diabetes insipidus ($P<0.0001$). A total of 104 patients (4%) had received treatment with radiotherapy.

Overall morbidity

In the whole cohort of NFPA patients, the incidence of type 2 diabetes mellitus and sepsis was more than doubled compared with the general population (Fig. 1 and Table 2). The incidence of cerebral infarction was increased by over 60%, whereas the incidence of myocardial infarction was only slightly elevated compared with that expected. The incidence of fracture was increased by over 40% for the patients.

In the subgroup of patients treated ($n=104$) with radiation therapy, seven patients had a cerebral infarction compared with the expected number of 3.5 ($P=0.14$).

Men and women

The incidences (SIR, 95% CI) of type 2 diabetes mellitus (women 2.9, 2.4–3.6 vs men 2.2, 1.8–2.5; $P=0.016$) and cerebral infarction (women 2.3, 1.9–2.8 vs men 1.3, 1.1–1.6; $P<0.0001$) were significantly higher in women than in men (Table 2). Furthermore, the incidences of myocardial infarction and fracture were increased for women, whereas they were as expected for men. There

Figure 1

Morbidity in non-functioning pituitary adenomas presented as standardised incidence ratios and 95% CIs in the whole cohort and sub-grouped according to gender.

Table 2 Standardised incidence ratios for patients with non-functioning pituitary adenoma.

Morbidity	No. expected	No. diagnosed	SIR (95% CI)	P-value
Type 2 diabetes mellitus (<i>n</i> =2795) ^a	109.8	268	2.44 (2.16–2.75)	<0.0001
Men (<i>n</i> =1502)	71.8	156	2.17 (1.84–2.54)	<0.0001
Women (<i>n</i> =1293)	38.0	112	2.95 (2.43–3.55)	<0.0001
Myocardial infarction (<i>n</i> =2795)	150.2	177	1.18 (1.01–1.36)	0.036
Men (<i>n</i> =1502)	106.9	105	0.98 (0.80–1.19)	0.91
Women (<i>n</i> =1293)	43.3	72	1.66 (1.30–2.09)	<0.0001
Cerebral infarction (<i>n</i> =2795)	129.2	214	1.66 (1.44–1.89)	<0.0001
Men (<i>n</i> =1502)	83.5	110	1.32 (1.08–1.59)	0.006
Women (<i>n</i> =1293)	45.7	104	2.28 (1.86–2.76)	<0.0001
Patients treated with RT (<i>n</i> =104) ^b	3.5	7	1.98 (0.79–4.07)	0.14
Patients not treated with RT (<i>n</i> =2369) ^b	91.4	135	1.48 (1.24–1.75)	<0.0001
Sepsis (requiring hospitalization) (<i>n</i> =2795)	62.5	143	2.29 (1.93–2.70)	<0.0001
Men (<i>n</i> =1502)	43.1	92	2.13 (1.72–2.62)	<0.0001
Women (<i>n</i> =1293)	19.4	51	2.64 (1.96–3.46)	<0.0001
Fracture (<i>n</i> =2795)	211.6	305	1.44 (1.28–1.61)	<0.0001
Men (<i>n</i> =1502)	98.7	105	1.06 (0.87–1.29)	0.55
Women (<i>n</i> =1293)	113.0	200	1.77 (1.53–2.03)	<0.0001

RT, radiotherapy. ^aAnalysed on first diagnosis in the registry; ^bFor patients with NFPA diagnosed between 1 January 1997 and 31 December 2011.

was no significant difference for the incidence of sepsis requiring hospitalization between the genders (women 2.6, 2.0–3.5 vs men 2.1, 1.7–2.6; $P=0.24$).

Women with hypopituitarism and/or DI had an increased incidence of myocardial infarction, which was not seen for women without hormonal deficiencies (Table 3). Also, the incidence of cerebral infarctions was higher in women with hormonal deficiencies compared with non-deficient women (SIR 2.8, 95% CI: 2.2–3.6 vs 1.7, 1.2–2.3; $P=0.015$). There was no statistically significant difference in the incidence of sepsis between women with and without hormonal deficiencies (3.3, 2.3–4.6 vs 1.9, 1.1–3.0; $P=0.077$). Men without hormonal deficiencies had a worse outcome with respect to type 2 diabetes mellitus, myocardial infarction and fracture compared with men with hypopituitarism and/or DI.

Young age at diagnosis

For patients who were diagnosed with NFPA before or at 40 years of age the incidences of type 2 diabetes mellitus, cerebral infarction and sepsis requiring hospitalization were clearly increased compared with the general population (Table 4). Women diagnosed at a young age had an increased incidence of type 2 diabetes mellitus, which was not seen for men.

Discussion

This nationwide study demonstrated an increased incidence of type 2 diabetes mellitus, myocardial infarction,

cerebral infarction, sepsis and fractures in patients with NFPA compared with the general population. The study, the largest one of patients with NFPA to date, provides a new insight into the condition and stresses the importance of early detection and adequate preventive management of comorbidities in patients with NFPA.

Women with pituitary insufficiency have a higher mortality ratio than men (1, 2, 3, 5, 14). In accordance with previous studies on mortality, women with NFPA seem to be especially vulnerable for comorbidities. In fact, women in our cohort had excess incidences of myocardial infarction and fractures, whereas men did not. Also, the increased incidences of diabetes mellitus and cerebral infarction that were observed in both genders were significantly higher in women than in men. The reason for these gender differences is unclear although results from previous studies indicate that relatively higher glucocorticoid doses in women (glucocorticoid dose per kg body weight), untreated growth hormone deficiency and the quality of sex steroid replacement may be influencing factors (2, 15, 16). It has also been suggested that the natural survival advantage that women have over men disappears with pituitary insufficiency (5) and that hypopituitarism is more often underdiagnosed in women compared with men (17). In the current study, more men than women were diagnosed with pituitary insufficiency. Thus, underdiagnosis, and thereof undertreatment, may contribute to the differences observed between the genders.

The cohort in the current study included 423 patients diagnosed with NFPA at or before the age of 40 years. In accordance with previous epidemiological studies on

Clinical Study	D S Olsson and others	Morbidity in patients with NFPA	175:1	59
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Table 3 Morbidity in patients with non-functioning pituitary adenoma with and without hormonal deficiencies.

Morbidity	No. expected	No. diagnosed	SIR (95% CI)	P-value
Type 2 diabetes mellitus ^a				
Men				
With hypopituitarism and/or DI (<i>n</i> =957)	51.9	94	1.81 (1.46–2.22)	<0.0001
Without hypopituitarism and/or DI (<i>n</i> =545)	19.9	62	3.11 (2.38–3.99)	<0.0001
Women				
With hypopituitarism and/or DI (<i>n</i> =572)	20.7	66	3.19 (2.47–4.06)	<0.0001
Without hypopituitarism and/or DI (<i>n</i> =721)	17.3	46	2.66 (1.95–3.55)	<0.0001
Myocardial infarction				
Men				
With hypopituitarism and/or DI (<i>n</i> =957)	77.1	63	0.82 (0.63–1.05)	0.12
Without hypopituitarism and/or DI (<i>n</i> =545)	29.8	42	1.41 (1.01–1.90)	0.041
Women				
With hypopituitarism and/or DI (<i>n</i> =572)	23.3	45	1.93 (1.41–2.58)	<0.0001
Without hypopituitarism and/or DI (<i>n</i> =721)	20.0	27	1.35 (0.89–1.96)	0.16
Cerebral infarction				
Men				
With hypopituitarism and/or DI (<i>n</i> =957)	59.9	75	1.25 (0.98–1.57)	0.066
Without hypopituitarism and/or DI (<i>n</i> =545)	23.6	35	1.48 (1.03–2.06)	0.034
Women				
With hypopituitarism and/or DI (<i>n</i> =572)	24.6	69	2.80 (2.18–3.55)	<0.0001
Without hypopituitarism and/or DI (<i>n</i> =721)	21.1	35	1.66 (1.16–2.31)	0.0068
Sepsis (requiring hospitalization)				
Men				
With hypopituitarism and/or DI (<i>n</i> =957)	30.5	65	2.13 (1.64–2.72)	<0.0001
Without hypopituitarism and/or DI (<i>n</i> =545)	12.6	27	2.14 (1.41–3.12)	0.0004
Women				
With hypopituitarism and/or DI (<i>n</i> =572)	10.3	34	3.29 (2.28–4.59)	<0.0001
Without hypopituitarism and/or DI (<i>n</i> =721)	9.0	17	1.89 (1.10–3.02)	0.017
Fracture				
Men				
With hypopituitarism and/or DI (<i>n</i> =957)	69.7	61	0.88 (0.67–1.12)	0.29
Without hypopituitarism and/or DI (<i>n</i> =545)	29.0	44	1.52 (1.10–2.04)	0.0090
Women				
With hypopituitarism and/or DI (<i>n</i> =572)	59.7	103	1.73 (1.41–2.09)	<0.0001
Without hypopituitarism and/or DI (<i>n</i> =721)	53.3	97	1.82 (1.48–2.22)	<0.0001

DI, diabetes insipidus. ^aAnalysed on first diagnosis in the registry.**Table 4** Morbidity in 423 young adult (age ≤40 years) patients with non-functioning pituitary adenoma.

Morbidity	No. expected	No. diagnosed	SIR (95% CI)	P-value
Type 2 diabetes mellitus ^a				
Young adult patients	1.9	9	4.62 (2.11–8.77)	0.0004
Men (<i>n</i> =173)	1.1	4	3.58 (0.98–9.16)	0.054
Women (<i>n</i> =250)	0.8	5	6.02 (1.95–14.1)	0.0033
Myocardial infarction				
Young adult patients	1.3	1	NC	NC
Cerebral infarction				
Young adult patients	0.9	5	5.75 (1.87–13.4)	0.0040
Sepsis (requiring hospitalization)				
Young adult patients	1.4	5	3.65 (1.18–8.51)	0.026
Fracture				
Young adult patients	8.8	6	0.68 (0.25–1.48)	0.44
Men (<i>n</i> =173)	5.2	1	NC	NC
Women (<i>n</i> =250)	3.7	5	1.37 (0.44–3.19)	0.61

NC, not calculated. ^aAnalysed on first diagnosis in the registry. If the number of events was five or less, figures were not divided depending on gender.

mortality in patients with hypopituitarism (3, 6), young patients with NFPA were shown to be especially exposed with 3 to 6 times increased incidences of type 2 diabetes mellitus, cerebral infarction and sepsis. Even though the number of individual cases with these comorbidities was relatively small, and the 95% CIs were consequently wide, preventive measures for patients diagnosed with NFPA at young age should not be underestimated.

Hypopituitary patients have excess vascular mortality and increased occurrence of the metabolic syndrome, diabetes mellitus, cardiac diseases and non-fatal stroke (1, 2, 3, 16, 18, 19). The reason for this is probably multifactorial, with non-physiologic glucocorticoid replacement, untreated growth hormone deficiency and undertreatment with sex steroids being suggested explanations (2, 20). Our results, showing higher incidences of type 2 diabetes mellitus, myocardial infarction and cerebral infarction among patients with NFPA, are in line with previous studies. Pituitary function only seemed to influence the outcome in women, but not in men. In fact, the incidence ratios in women for myocardial and cerebral infarctions were negatively affected by pituitary insufficiencies, whereas the incidences of type 2 diabetes mellitus were not affected. Furthermore, men without hypopituitarism had higher incidences of type 2 diabetes mellitus than men with pituitary insufficiency. Other factors, yet unidentified, must, therefore, be involved in the development of adverse outcome in patient with NFPA. Further studies are needed to illuminate which factors influence cardiovascular outcome in patients with NFPA, not only the influence of pituitary hormone replacement but also the impact of factors such as socioeconomic status, physical activity, dietary habits and cognitive function.

An interesting finding in this study was the higher incidence of sepsis requiring hospitalization in both men and women with NFPA. Awareness of this increased risk is of great importance, especially for patients with secondary adrenal insufficiency. In fact, previous study has shown a significant increased mortality in hypopituitary patients due to infectious diseases and that all of the patients who died were ACTH insufficient (21). In our study, the incidence of sepsis was not different between patients with pituitary insufficiency and those with normal pituitary function. Although not statistically significant, sepsis tended to be more common in hypopituitary women compared with female patients with intact pituitary function ($P=0.077$).

Patients with pituitary insufficiency have decreased bone mineral density and increased fracture risk (22, 23, 24). In the current study, we demonstrate that women with NFPA have an almost two-fold increased incidence of

fractures compared with the background population, while men did not have an increased risk. Interestingly, no difference in incidence of fracture was seen when women with and without pituitary insufficiency were compared with each other.

The main strength of the study is the large number of patients included, with more than 20 000 patient-years of follow-up, which makes the study the largest so far on patients with NFPA. Also, the identification process with multiple inclusion and exclusion criteria as well as an internal validation of the NFPA diagnosis in 17% of the patients showing that over 90% had a correct diagnosis, which is a high proportion, adds to the strengths of the study. However, there were also some limitations. Due to the nature of the study, based on registry data, detailed information on tumour treatment and the degree of hypopituitarism and its management were not available in the registry. Thus, the role of glucocorticoid, growth hormone, sex hormone and L-thyroxin replacement therapy on the comorbidities could not be analysed and the results concerning hormonal status should, therefore, be interpreted with caution. However, the validity of the variable "pituitary insufficiency" has been investigated previously in patients with craniopharyngioma with reassuring results (12).

In conclusion, this nationwide study demonstrates an excessive morbidity due to type 2 diabetes mellitus, myocardial infarction, cerebral infarction, sepsis and fracture in patients with NFPA. Also, women and young adults with NFPA seem to be especially vulnerable to develop comorbidities. The results emphasize the importance of an active surveillance in all patients diagnosed with NFPA as well as adequate preventive treatments in high-risk patients.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-16-0173>.

Declaration of interest

D S O has been a consultant for Novartis, Ipsen and Pfizer. I L B and O R have nothing to disclose.

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Author contributions statement

All authors took part in the design of the study. D S O and I L B performed the patient selection process and data collection. D S O designed the figure. All authors contributed to data interpretation and analysis, and in writing and revising the report. All authors are responsible for the integrity of the data and accuracy of the analysis, and all approved the final report.

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