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Estimating diagnostic delay in patients with pituitary adenomas in Sweden: a cross-sectional study

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ABSTRACT

Objective A delayed diagnosis of pituitary adenomas (PAs) can lead to increased morbidity and reduced quality of life. The aim was to estimate diagnostic delay and investigate the concordance between patient-reported symptoms and the medical record documentation in patients with PA.

Design Cross-sectional study.

Setting Seven university hospitals.

Participants 654 patients: non-functioning PA (NFPA, 314), prolactinoma (118), acromegaly (164) and Cushing's Disease (CD, 58).

Data collection Questionnaires and medical record extraction.

Primary and secondary outcomes Type of first healthcare contact, delay of PA diagnosis and patient-reported symptoms and symptoms documented in medical records.

Results First healthcare contact was usually a general practitioner. Estimated time from symptoms to diagnosis varied from <1 year (66%), 1–5 years (12%), 5–9 years (13%) and >10 years (9%). The longest diagnostic delays were observed in acromegaly and CD. A longer delay was observed in women compared with men (p<0.001). The most frequent patient-reported symptoms among NFPA were headache and visual disturbances; for prolactinomas, menstrual irregularities and headache; for acromegaly, change in appearance and snoring; and for CD, weight gain and tiredness. Concordance between patient-reported symptoms at diagnosis and medical records was found for visual disturbances in NFPA and prolactinomas (*Cohen's* kappa >0.6) and for menstrual irregularities in prolactinomas (*Cohen's* kappa >0.7).

Conclusion We report a large variation in symptom duration before diagnosis with a substantial diagnostic delay in patients with CD and acromegaly. An increased awareness about endocrine diseases in the general population and health professionals may contribute to earlier diagnosis of pituitary adenomas.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Large study including 654 patients with pituitary adenomas.
⇒ The only study covering patients with different types of pituitary adenomas contributing both to identify common and tumour-specific symptoms.
⇒ Including the patient's perspective could provide valuable insights into the factors contributing to diagnostic delay in pituitary adenomas.
⇒ A limitation of the study is the retrospectively collected patient-reported information.

INTRODUCTION

Pituitary adenomas (PA) are a diverse group of tumours arising from the pituitary gland. These adenomas are slow-growing and have an estimated incidence of about 4/100 000 inhabitants per year.[1 2] Pituitary adenomas are benign tumours from hormone-expressing cells in the pituitary gland. Depending on their hormonal activity, they are categorised as hormone-secreting, such as prolactinomas, acromegaly and Cushing's disease (CD) and non-secreting (non-functioning pituitary adenomas, NFPA). According to size, they are classified as macroadenomas (≥1 cm) or microadenomas.[3 4]

The diagnosis of PA is often delayed as symptoms and signs often develop slowly. Some symptoms, such as headache, visual disturbances and symptoms of hypopituitarism/hormone hypersecretion, may raise the suspicion of a PA, whereas other symptoms such as fatigue, weight gain or depression are unspecific.[5 6] Thus, a definitive diagnosis is often made years after the onset of the pituitary disease. In primary care, common symptoms such as weight gain and tiredness usually have other causes, and a rare disease such as PA may not be considered among the differential diagnoses.

In some pituitary diseases, a delayed diagnosis can lead to higher mortality and morbidity, such as cardiovascular disease.[7 8] Further, impaired quality of life has also been reported.[9] Timely diagnosis and appropriate treatment with surgical removal

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and/or pharmacological treatment can be improved as it is important to avoid consequences such as blindness, infertility and fatigue. Further, tumour size is an important predictor of surgical outcome and complications. In acromegaly, a higher proportion of macroadenomas than microadenomas have been reported,[10] which may reflect a diagnostic delay. Previous studies have reported 2.5 to 5.9 years from symptom onset to diagnosis in patients with acromegaly,[11–13] including a 0.9–2 years longer diagnostic delay in women than in men.[14 15] Further, in patients with CD, a confirmed median delay of 2 years between symptom onset and diagnosis has been reported.[16]

The patients' own report of the symptoms combined with the healthcare providers' documentation in the medical records is central in clinical medicine. Previous research suggests that symptoms are often underreported by patients[17 18] and that patient's report of symptoms is not in accordance with medical record documentation in patients with other chronic conditions than PA.[19 20]

Studies investigating the latency between the patients first experience of symptoms and the final diagnosis, including the symptoms reported compared with the symptoms documented in the medical record, are scarce. Identifying factors associated with diagnostic delay in PA may help non-specialists to recognise the disease. The present study aims to estimate the diagnostic delay in patients with PA. To improve early identification of patients with PA, we aimed to investigate the concordance between patient-reported symptoms and the medical record documentation and to identify the type of medical professionals who first recognised the symptoms leading to diagnosis.

METHODS

Participants

The Swedish Pituitary Register (SPR) is a quality register supported by the government and organised by a multidisciplinary network of endocrinologists, oncologists, neurosurgeons, neuroradiologists, pathologists and endocrine nurses from seven university hospitals in Sweden. A total of 7293 patients diagnosed with PA between 1991 and 2017 in Sweden were reported in SPR. A consecutive series of patients with PA reported in SPR and attending a scheduled visit to the endocrine nurses at the departments of Endocrinology in seven University Hospitals in Sweden were invited to participate at one time point per patient during a 3 year period (2014–2017). Patients with severe cognitive dysfunction and inability to complete the questionnaire or not able to understand Swedish were excluded. Very few patients declined participation.

Patient and public involvement

Patients and the public were not involved in the preparation of the study design.

Data collection

Patient data was collected from a patient-reported questionnaire developed by endocrine nurses and endocrinologists, medical records and SPR. Patients were invited to complete a questionnaire including questions regarding age at first symptoms, experience of first symptoms, age at diagnosis, symptoms at diagnosis, first healthcare contact and level of education at one time point after diagnosed with PA. The authors used a structured form including symptoms (figure 2A–D) that brought the patient to seek healthcare, age at diagnosis, micro/macroadenoma, visual disturbances (visual field defect, visual impairment), pituitary function, comorbidities and which medical care the patients visited and when before the PA diagnosis. At the last part of the patient-reported questionnaire, the patients had the possibility to express in free text their experience of having symptoms and the impact of the diagnostic delay. An inductive qualitative study design was conducted and presented as themes based on the patients' experience. This process involves reviewing data repeatedly, identifying common themes and developing a broader understanding of the subject being studied. Two authors independently reviewed and coded the answers: CF and MF. Three other authors reviewed the codes: BE, BEE and CD.

Statistical analysis

Diagnostic delay from symptoms to final diagnosis is presented as median and range (years). The IQR is defined as the difference between the third quartile (Q3) and the first quartile (Q1). The Mann–Whitney *U* test was used to compare duration from symptom onset to final diagnosis between men and women and between different types of PA. The time of onset of symptoms was collected from the patient questionnaire and the time of final diagnosis from the medical records. Bivariate correlations were assessed using the Spearman rank correlation coefficient. A P value <0.05 was regarded as statistically significant. To investigate the extent to which symptoms experienced by patients were recognised by their doctors, two binary variables were analysed. The first variable reflected the symptoms reported in the patient questionnaire and the second reflected symptoms reported in the medical records. Kappa statistics were used to quantify the level of agreement according to which symptoms experienced by patients were also recognised by their doctors: <0.20, poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement.[21] Calculations were made using SPSS version 29, and results were regarded as statistically significant if p<0.05.

RESULTS

Patient characteristics

A total of 654 patients (333 men, 321 women) with pituitary adenoma were included in the study. Median age at inclusion was 61 (range 19–92) years for men and

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Table 1 Patient characteristics in 654 patients diagnosed with pituitary adenoma

	Men/ women (n)	Age median years (range)		Adenoma size macro/ micro		Visual disturbances*	Pituitary insufficiency at diagnosis† n
		Men	Women	Men N	Women N	Men/women n	
All patients	335/322	61 (19–92)	52 (18–91)	261/62	179/119	226/159	20
NFPA	187/127	66 (19–92)	62 (22–91)	151/22	105/13	180/124	16
Prolactinoma	58/60	55 (19–77)	33 (23–79)	42/14	0/44	23/18	4
Acromegaly	83/81	59 (24–81)	58 (18–84)	62/16	46/27	21/16	2
CD	10/48	60 (43–70)	48 (21–76)	2/8	10/34	2/1	0

*Visual field defect or visual impairment.
†≥ 3 hormone deficiencies.
CD, Cushing's disease; n, number; NFPA, non-functioning pituitary adenoma.

52 (range 18–91) years for women. In all, 62 men and 119 women presented with microadenoma and 261 men and 179 women with macroadenoma (missing data in 33 patients). The distribution of type of PA, age, micro/macroadenoma, visual field defect, visual impairment and pituitary insufficiency at diagnosis is shown in table 1.

Among all patients, 280 reported an academic education, 250 upper secondary school and 139 elementary school.

Time to PA diagnosis

The median diagnostic delay from the patients' report of onset of symptoms to the final diagnosis was 1 year (range 0–44). The same diagnostic delay was reported in the medical record for the first healthcare contact to diagnosis. The patients were divided into four different groups based on the diagnostic delay between the patients' report of onset of symptoms to the diagnosis (table 2).

The cohort was positively skewed with approximately half of the patients diagnosed within a year (50th percentile), 75% <5 years and 87.5% <10 years and the remaining 12.5% had >10 years of delay before diagnosis. The missing patient-reported data was due to not remembering age at diagnosis. A significant difference in median diagnostic delay of symptoms to the final diagnosis was found between men and women; 1 year (range 0–31, IQR 4 years) for men and 2 years (range 0–44, IQR 6 years) for women, p<0.001. When analysing these gender differences across various PA subgroups, no significant differences were observed; however, there was a trend for more pronounced gender differences in patients with acromegaly and CD. The median diagnostic delay for patients with acromegaly, 4 years (range 0–32), was significantly longer than for NFPA, median 1 year (range 0–20), p<0.001. Patients with prolactinomas had a median diagnostic delay of 2 (range 1–19) years and in CD 4 (range 2–19) years, not significantly different to other types of PA (figure 1). Among CD, the patients with microadenomas at diagnosis had a significantly longer diagnostic delay from symptom onset, median 4 (range 0–19) years, compared with patients with macroadenomas, 2 (range 0–10) years, p=0.03. No clear differences in this delay were found between patients with micro- or macroadenoma at diagnosis among the other types of PA.

Diagnostic delay and age

Among all patients, older age at diagnosis was significantly correlated to longer delay from the first healthcare contact to the final diagnosis (r=0.5, p=0.002) and the delay from the first symptom to the final diagnosis (r=0.5, p=0.03). Within the prolactinoma group, older age at diagnosis was significantly correlated to the delay of first symptom to the final diagnosis (p=0.03), but not to the first healthcare contact. For patients with NFPA, acromegaly and CD, there was no significant correlation between age and duration of symptoms to the first health contact.

Table 2 Duration of symptoms to diagnosis according to patient's reports (missing data n=119)

First symptom to diagnosis	0–1 year n (%)	2–4 year n (%)	5–9 year n (%)	10–44 year n (%)
All patients n=535	357 (67%)	61 (11%)	68 (13%)	49 (9%)
NFPA n=257	199 (77%)	32 (12%)	16 (6%)	10 (4%)
Prolactinoma n=95	56 (59%)	24 (25%)	10 (11%)	5 (18%)
Acromegaly n=133	66 (50%)	20 (15%)	23 (17%)	24 (18%)
CD n=50	21 (42%)	15 (30%)	8 (16%)	6 (12%)

CD, Cushing's disease; n, number; NFPA, non-functioning pituitary adenoma.

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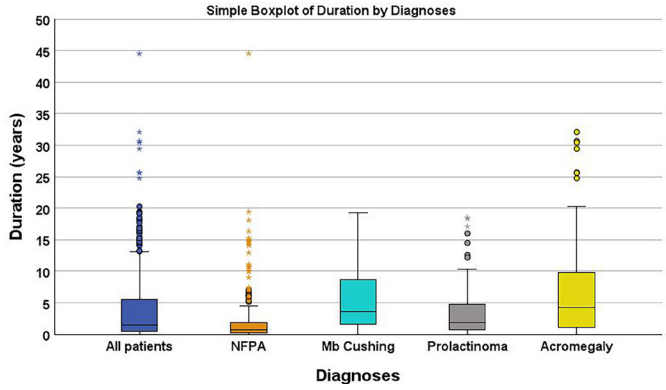

Figure 1 Duration from first symptom to diagnosis in 535 patients with pituitary adenomas. NFPA, non-functioning pituitary adenoma.

Frequently reported symptoms

Among NFPA frequently reported patient symptoms were headache, visual disturbances and tiredness (figure 2A); for prolactinomas, menstrual irregularities, headache and tiredness (figure 2B); for acromegaly, change in appearance, snoring, headache (figure 2C); and for *CD,* weight gain, tiredness and weakness (figure 2D).

Concordance between patient-reported symptoms and doctors' recognition of symptoms

To compare the extent to which symptoms experienced by patients are recognised by their doctors, two binary variables were analysed. Substantial agreement between patient report and medical record was found for visual disturbances in NFPA (figure 2A) and prolactinomas (figure 2B) (*Cohen's* kappa >0.6) and for menstrual irregularities in prolactinomas (figure 2B) (*Cohen's* kappa >0.7). In prolactinomas, we found poor agreement for galactorrhoea (figure 2B) and in acromegaly for weakness and tiredness (figure 2C). These symptoms were more frequently reported by the patients than in the medical records. In *CD,* we found no agreement regarding weakness and dizziness (figure 2D), which was more frequently reported by patients compared with medical records. We also report poor agreement for hirsutism, more frequently reported in medical records compared with the patient questionnaire (figure 2D).

Self-reported diagnoses

There was some discrepancy between the patients' self-reported diagnoses of the pituitary disease compared with the endocrinologists' medical records. Thus, 228 patients reported NFPA (*vs* 314 by endocrinologists), 101 prolactinoma (*vs* 118), 154 acromegaly (*vs* 164) and 57 CD (*vs* 58). 72 patients reported their diagnoses as unknown, and among these, 62 patients were diagnosed with NFPA, nine with acromegaly and one patient was diagnosed with CD.

First healthcare contact

The patients' perspective shows for prolactinomas GP as the first healthcare contact (53%), followed by gynaecologists (26%); for acromegaly, GP was the first contact (32%), followed by the dentist (6%); for NFPA, ophthalmologist was the first healthcare contact (22%), followed

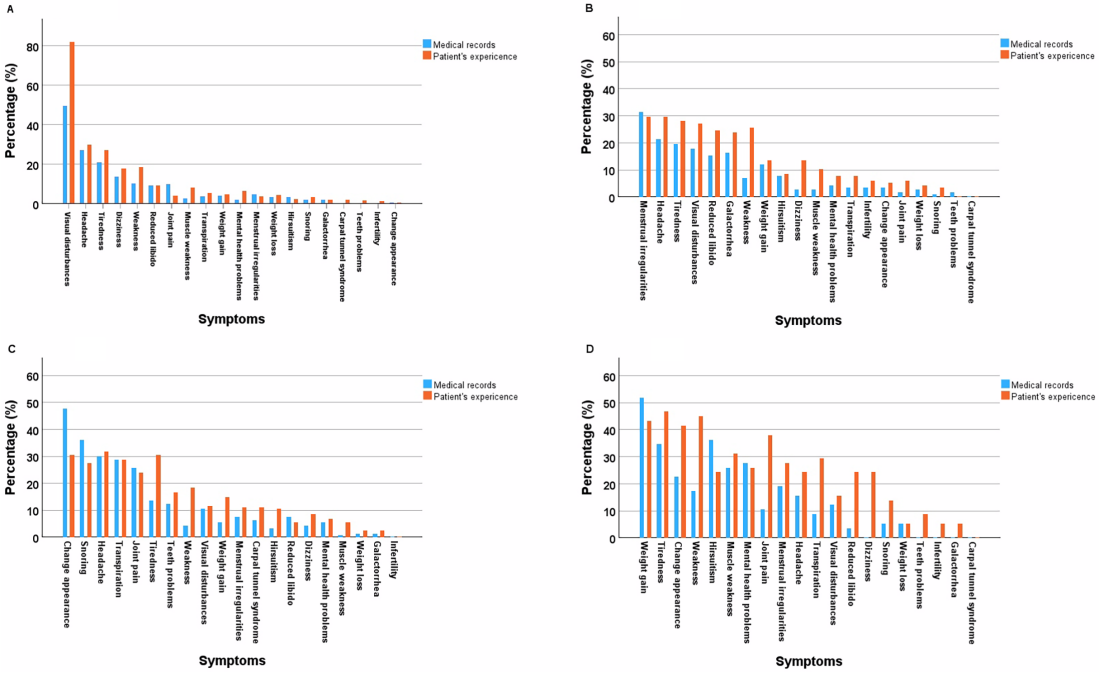

Figure 2 Experience from 54 patients with pituitary adenomas in relation to medical record data. (A) Experience from 314 patients with NFPA in relation to medical record data. (B) Experience from 118 patients with prolactinoma in relation to medical record data. (C) Experience from 164 patients with acromegaly in relation to medical record data. (D) Experience from 58 patients with Cushing's disease in relation to medical record data.

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by the GP (16%); and for CD, GP as the first contact (40%).

Comorbidities at follow-up

Hypertension was most frequent among patients with CD (52%), followed by NFPA (24%) and acromegaly (23%). A diagnosis of diabetes was found in 23% of patients with CD and 7% of patients with acromegaly and osteoporosis in 12% of the patients with CD.

Level of education

In the present study, we didn't find a significant difference between the duration of symptoms to the diagnosis and patients with or without education at the university level.

Patients' experience

50% of the participants expressed in free text their experience of having symptoms and the impact of the diagnostic delay. The qualitative analysis resulted in two categories: suffering *from subtle symptoms with a feeling that something is wrong* and *unawareness among healthcare professionals*.

Suffering from subtle symptoms and a feeling that something is wrong

The patients highlighted the burden of symptoms such as pain, fatigue and weakness. They had been suffering from subtle symptoms for many years and struggled with a feeling that something was wrong.

> I had joint pain for many, many years. First when I had complaint of bone growth a clinical investigation started.
>
> (Man with acromegaly, delay 11 years)
>
> I had headache and fatigue for many years and was diagnosed with Hortons headache. I was referred to a MRI and the pituitary adenoma was not visible. Several years later I had another MRI and was finally diagnosed with Prolactinoma.
>
> (Woman with prolactinoma, delay 17 years)
>
> I was seeking care for heavy thirst and fatigue, I fell asleep during dinner. I have always been tired and weak and I suspect I had this tumour for a long time.
>
> (Man with CD, delay 1 year)

Unawareness among healthcare professionals

The participants also expressed the long pathway from first symptoms to diagnosis, including their experience of not being listened to. They had experience from a long way through several healthcare contacts, and no one seemed to have knowledge about PA. They not only had a feeling of being treated with ignorance when seeking care but also highlighted the lack of capturing the whole picture.

> Tests were taken, first for breast cancer, followed by some additional blood tests. The prolactin level was extremely high. "The lab must have made a mistake," the doctor said. New tests were done, showing the same high levels, leading to a referral to an endocrinologist. The eye issue led to an eye examination and eventually a diagnosis of ocular migraine. I realized after starting medication that many other symptoms were also linked to the prolactinoma: fatigue, decreased libido, changes in body hair, and weight gain. All of these symptoms gradually disappeared within a year.
>
> (Woman with prolactinoma, delay 3 years)
>
> I was referred to the cardiologist for impaired strength, then to the hematologist for low haemoglobin, then the rheumatologist for joint pain and finally to the endocrinologist.
>
> (Man with NFPA, delay 2 years)
>
> My symptoms, such as diabetes and high blood pressure, were treated for 3 years, before the physician initiated a clinical investigation.
>
> (Man with acromegaly, delay 5 years)
>
> During the years from first symptoms to diagnosis I was referred to different specialists. They showed no interest in helping me, as they couldn't find a diagnose. Subsequently, I developed diabetes, high blood pressure, depression etc. I read about hormone secreting adenomas and asked for a MRI. I am very disappointed over the lack of interest from the physicians.
>
> (Man with CD, delay 7 years)

DISCUSSION

We report a considerable and variable diagnostic delay in patients with PA, with emphasis on the longer delay observed in women. Half of the study participants waited over a year for a diagnosis, and of those, 25% experienced a diagnostic delay of over 5 years. Our study shows that the identification of PA is a significant challenge. Visual disturbances and menstrual irregularities showed substantial agreement between the endocrinologists' documentation and patient-reported data, whereas weakness, tiredness and dizziness showed poor agreement. The most frequent entry to diagnosis was general practitioners.

Potential reasons for the gender difference may include differences in symptom manifestation, degree and severity of symptoms, healthcare-seeking behaviour or healthcare provider biases. Studies have reported that women with PA may experience more varied and non-specific symptoms, making it challenging for patients, as well as physicians, to recognise the underlying diagnosis.[22] Women seem to be more likely to dismiss their symptoms, delay the seeking of medical help or experience barriers in accessing healthcare services.[1] In addition, healthcare provider gender biases can contribute to diagnostic delays. Patient gender can influence physicians' management strategies when assessing symptoms.[23 24]

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Further, the psychosocial situation may have an impact on the duration between symptoms and diagnosis, as an association between lower socio-economic status and more severe disease at time of diagnosis, including larger tumour size, has been reported in patients with NFPA.[25] In the present study, we didn't find a significant difference between the duration of symptoms to diagnosis and patients with or without education at university level, but we lack information about income or other socio-economic-related factors. Another factor influencing the diagnostic delay might be age, as elderly patients often consider symptoms as normal ageing.[26–28] Jahangiri *et al*[6] investigated 75 patients with NFPA and found a duration of visual disturbances from 1 week up to 15 years and that older age was associated with diagnostic delay.[6] This is in line with our results showing that older age at diagnosis is associated with longer duration of symptoms, as well as first healthcare contact, to final diagnosis.

Our study also investigated the concordance between the endocrinologists' documentation in medical records and patient-reported data of the symptoms and diagnosis. Visual disturbances and menstrual irregularities showed substantial agreement between the endocrinologists and patients, indicating a high degree of concordance to concrete symptoms. Conversely, diffuse symptoms such as weakness, tiredness and dizziness showed poor concordance between endocrinologists' documentation and patient-reported data. The discordance in reporting these symptoms indicates the challenge in capturing and interpreting subjective symptoms in a clinical setting. The variability and poor concordance in documenting symptoms may be influenced by individual patient perceptions, communication barriers or the inherent subjectivity of these symptoms[29] and highlights the complexity of diagnosing pituitary adenomas. It underscores the importance of developing more standardised approaches to assess and document these symptoms.

In patients with NFPA, the most frequently reported symptom was visual disturbances. Thus, 81% of the patients reported visual disturbances, but only 49% had documented visual disturbances in the medical records. Self-reported medical history data may differ from medical record data due to poor patient–clinician communication, symptoms caused by other diseases, habituation to symptoms, absence of satisfactory explanation of symptoms or health literacy of the patient,[19 20] including a tendency to report symptoms of recent onset and greater severity. Factors relevant to care providers may be time pressure or bias, such as reporting only the cardinal symptoms.[30]

The present study is one of the largest with 654 patients included and the only study covering patients with different subtypes of PA. Furthermore, presenting the patient's perspective adds another dimension to the study. A limitation of the study is the risk of recall bias regarding patient-reported data about the first experience of symptoms, which may include difficulties in remembering the time points of symptom onset. Nonetheless, the duration of symptoms until diagnosis among these patients is considerable, with a median delay of 4 years for patients with acromegaly, up to a maximum of 44 years in the present study. Another limitation is the lack of validation of the questionnaire. The questionnaire focused on known physical and psychological symptoms in connection with the diagnosis of adrenocorticotropic hormone-secreting, growth hormone-secreting, prolactin-secreting or non-secreting pituitary adenomas. The questions were developed by an expert panel of endocrinologists and endocrine nurses.

Missing data on the size of the adenoma was due to not being able to find information on this in the medical record or in the register. This was also true for other information extracted from medical records. The patient-reported information was in some cases not complete as the patients had missed completing all questions or could not recall and left the question empty.

The presented delay in the diagnosis of some pituitary adenoma subtypes raises important clinical implications. An increased awareness of symptoms from pituitary adenomas through increased information to the general population and directed education of healthcare professionals may contribute to earlier diagnosis. Further, it is also important to increase awareness that disorders like type 2 diabetes, sleep apnoea, carpal tunnel syndrome, hypertension and infertility could be caused by an underlying PA. Future research should explore these factors to enhance our understanding and develop standardised approaches to improve the accuracy and consistency of symptoms reported in clinical context.

CONCLUSIONS

We report a long diagnostic delay among patients with PA, significantly longer in women and in older patients. We suggest that increased information to the general population and directed education of health professionals may contribute to earlier diagnosis of pituitary adenomas.

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Contributors All endocrine nurses (MF, CD, CF, CA, HW and MW) contributed to the study by validating patients' diagnoses by review of medical records in their regions. MF and CD and CF were responsible for the study conception and design. CF and BE performed the data analyses and CF drafted the manuscript. All authors have read, commented on and approved the final manuscript. CF is the guarantor.

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Patient consent for publication Not applicable.

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