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Cushing's disease in Western Norway Regional Health Authority

ORIGINAL ARTICLE

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Background

Cushing's disease is caused by a pituitary adenoma that produces adrenocorticotropic hormone (ACTH), leading to overproduction of cortisol by the adrenal glands. The aim of the study was to investigate the incidence, clinical manifestation and treatment outcomes in Western Norway Regional Health Authority.

Material and method

The study is based on a retrospective review of medical records of patients diagnosed with Cushing's disease at Haukeland University Hospital in Bergen during the period 1 January 2010 to 31 December 2022.

Results

We identified 42 patients with Cushing's disease during the period 1 January 2010 to 31 December 2022. The incidence was estimated at 3.0 per million inhabitants per year. Thirty-three of the 42 patients had one or more metabolic disorders at the time of diagnosis. All underwent transsphenoidal pituitary surgery. Twenty-five of the 42 patients went into remission after the first or second operation. At the end of the study or at the time of death, 20 patients were in remission following pituitary surgery and/or Gamma Knife radiotherapy: 2 out of 7 with macroadenoma, 12 out of 21 with microadenoma, and 6 out of 14 with no conclusive findings from magnetic resonance imaging (MRI). Of the remaining 22 patients, 5 underwent bilateral adrenalectomy, while 13 had persistent disease at the end of the study or at the time of death. Long-term outcome data were missing for two patients, and two had recently undergone surgery with results still pending.

Interpretation

The incidence of Cushing's disease in Western Norway Regional Health Authority is higher than that reported in previous European studies. Treatment outcomes were associated with tumour characteristics, which highlights the need to tailor treatment strategies to the individual patient.

Main findings

The estimated incidence of Cushing's disease in Western Norway Regional Health Authority during the period 1 January 2010 to 31 December 2022 was 3.0 per million inhabitants per year.

Thirty-three of the 42 patients in the study had one or more metabolic disorders at the time of diagnosis. All patients underwent pituitary surgery as first-line treatment.

At the end of the study or at the time of death, 20 of the 42 patients were in remission following pituitary surgery and/or Gamma Knife radiotherapy.

Endogenous Cushing's syndrome is caused by adrenal adenoma, ectopic production of adrenocorticotropic hormone (ACTH), or Cushing's disease (ACTH-producing pituitary adenoma) (1). Cushing's disease is the most common, with a reported incidence of 0.7–2.4 per million inhabitants per year (1, 2). The main challenge is recognising the disease among other common health problems. Clinical signs include moon face, abdominal obesity and skin atrophy. Symptoms can include malaise, proximal muscle weakness and psychiatric problems. Many patients have accompanying high blood pressure, diabetes and osteoporosis (1, 3).

Diagnosis is challenging. Screening tests include 24-hour urinary cortisol measurement, evening salivary cortisol testing and the dexamethasone suppression test (1, 4). An ACTH value above 4.4 pmol/L in the morning indicates an ACTH-dependent cause (4). Magnetic resonance imaging (MRI) of the pituitary gland, corticotropin-releasing hormone (CRH) testing and inferior petrosal sinus catheterisation are used to differentiate ectopic ACTH production from Cushing's disease (1, 3, 4). MRI can reveal a pituitary adenoma, but the adenoma can be too small to detect (3). A CRH test showing more than a 50 % increase in ACTH and/or more than a 20 % increase in cortisol indicates Cushing's disease (5). Inferior petrosal sinus catheterisation compares ACTH levels in the venous sinus that drains the pituitary gland with levels in peripheral blood. A gradient greater than 2 before or greater than 3 after CRH stimulation suggests a pituitary cause (3).

The primary treatment for Cushing's disease is transsphenoidal pituitary surgery. In cases of persistent disease or relapse, treatment options can include reoperation, radiotherapy (fractionated external beam radiation therapy or Gamma Knife), medication or bilateral adrenalectomy. Medication is used when patients are awaiting other treatment or if surgery is contraindicated (1). Bilateral adrenalectomy is a last resort and requires lifelong hormone replacement therapy with corticosteroids (3).

The aim of the study was to investigate the incidence, clinical course, treatment and treatment outcomes of patients with Cushing's disease in Western Norway Regional Health Authority.

Material and method

Patients who received the ICD-10 diagnosis E24.0 Pituitary-dependent Cushing's disease at Haukeland University Hospital during the period 1 January 2010 to 31 December 2022 were included in the study. Data were obtained from medical records, and two of the authors verified the diagnoses.

The study includes patients from several hospitals in Western Norway Regional Health Authority with varying diagnostic investigations and follow-up, which resulted in missing data for some patients.

All patients initially underwent transsphenoidal pituitary surgery performed using a microsurgical technique. In patients with no MRI findings, the pituitary gland was surgically explored. If no findings were observed during surgery, vertical incisions were made in the pituitary.

Remission was defined as 1) morning serum cortisol below 55 nmol/L within seven days postoperatively, 2) suppression of morning cortisol to below 50 nmol/L after a low-dose dexamethasone suppression test during a postoperative check-up, or 3) the need for corticosteroid substitution more than six months postoperatively. Recurrence of Cushing's disease was defined as clinical and biochemical signs of hypercortisolism after remission (6, 7).

Haukeland University Hospital serves as a regional centre for pituitary surgery, enabling calculation of incidence rates. Incidence was estimated by dividing the total number of cases by the number of person-years, based on the average annual adult

population in Western Norway Regional Health Authority during the period 1 January 2010 to 31 December 2022 (*n* = 1,083,190) (8). The result is reported as cases per million inhabitants per year.

The Regional Committee for Medical and Health Research Ethics (REK South-East A) deemed the study a retrospective quality assurance study (REK number 493901). The study was reported to the data protection officer at Bergen Hospital Trust (eProtocol project ID 3516). Descriptive statistics were used to present categorical and continuous variables.

Results

A review of medical records identified 42 cases of Cushing's disease, resulting in an estimated incidence of 3.0 per million inhabitants per year (95 % confidence interval: 2.8–3.1) in Western Norway Regional Health Authority. The median follow-up time was 61 months (interquartile range 34–109).

Patient characteristics are shown in Table 1. The CRH test indicated pituitary ACTH production in 36 of 38 cases. The two patients with a negative CRH test had inconclusive MRI findings but were diagnosed with Cushing's disease based on positive inferior petrosal sinus catheterisation. Inferior petrosal sinus catheterisation indicated pituitary ACTH production in 35 of 39 cases. Among 14 patients with no conclusive MRI findings, 12 had a positive result from inferior petrosal sinus catheterisation.

The treatment outcomes after pituitary surgery and Gamma Knife radiotherapy are presented in Figure 1. All patients initially underwent transsphenoidal pituitary surgery performed using a microsurgical technique. A total of 25 patients went into biochemical remission after the first or second operation, but of these, four experienced recurrence after 28–48 months. The seven patients treated with Gamma Knife radiotherapy were followed for a median observation time of 19 months (interquartile range 7–48). One of the two patients who went into remission after Gamma Knife radiotherapy experienced recurrence after 16 months.

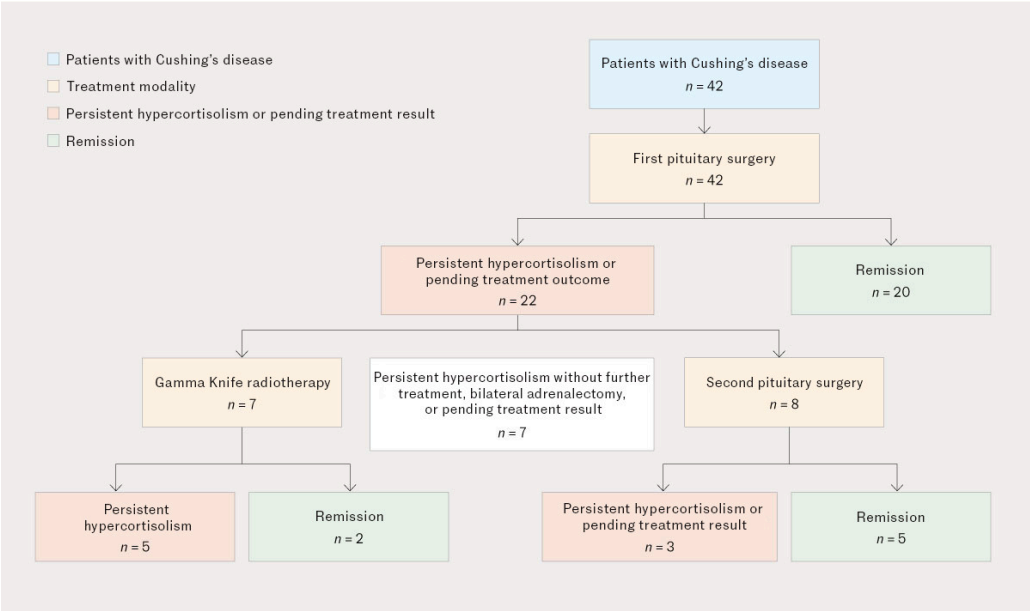

Figure 1 Flowchart showing the choice of treatment modalities and treatment outcomes. The figure illustrates only initial treatment outcomes following pituitary surgery and Gamma Knife radiotherapy, and does not include information on recurrence or remission status at the end of the study or at the time of death.

At the end of the study or at the time of death, 20 of the 42 patients were in remission following pituitary surgery or Gamma Knife radiotherapy. The remission rate was 2 out of 7 patients with macroadenoma (≥ 10 mm), 12 out of 21 patients with microadenoma (< 10 mm), and 6 out of 14 among patients with no conclusive findings on MRI. Five of the 42 patients (three with microadenoma and two with no conclusive MRI findings) underwent bilateral adrenalectomy. At the end of the study, 13 patients had persistent disease. Long-term outcome data were missing for two patients, and two had recently undergone surgery with results still pending.

After the first operation, 11 out of 42 patients experienced transient diabetes insipidus, compared to 2 out of 8 patients after the second operation. Following the first operation, 2 of the 42 patients developed cerebrospinal fluid leakage and 2 had persistent failure in one or more additional hormonal axes.

Of the 42 patients, 14 received cortisol-lowering medication at one or more points in time.

Discussion

The estimated incidence of Cushing's disease in Western Norway Regional Health Authority is higher than reported in previous European studies (2). Hypertension, obesity, hypercholesterolemia, osteoporosis and type 2 diabetes mellitus were common. All patients underwent transsphenoidal pituitary surgery as primary treatment. Pituitary surgery cured approximately half of the patients, while the remainder required either Gamma Knife radiotherapy, medication or adrenalectomy.

The remission rate was highest among patients with microadenoma, which is consistent with previous studies (6). We found slightly lower post-surgery remission rates compared with earlier literature, including a 2015 study from Oslo University Hospital, although the sample sizes are small (9, 10). This variation may be due to various factors, including differences in follow-up time and in the criteria used to define remission (7, 9). The number of patients without conclusive MRI findings and the number of macroadenomas extending into the cavernous sinus have a large impact on post-surgery remission rates.

Many patients who do not achieve complete biochemical remission after pituitary surgery can still experience a clinically significant reduction in the symptom burden. However, several patients with persistent hypercortisolism have not received further treatment due to comorbidities, patient choice or mild symptoms.

The results of our study show a surprisingly limited effect of Gamma Knife radiotherapy, in contrast to a multicentre study that reported sustained biochemical control in 57 % of patients (11). The effect often occurs late: one study reported a median time to normalisation of cortisol levels of 16 months (variation range 2–67) (12). The median follow-up time after Gamma Knife radiotherapy in our patients was 19 months (interquartile range 7–48).

Five patients in the study underwent bilateral adrenalectomy to cure hypercortisolism. In our assessment, this can often be a good solution and should probably be considered earlier for selected patients for whom it is difficult to control hypercortisolism.

The strength of the study is Haukeland University Hospital's role as a tertiary centre for pituitary surgery in Western Norway Regional Health Authority. Weaknesses include the retrospective design, which can result in incomplete data, as well as the challenge of measuring a very low incidence, since rare conditions yield few cases and a limited statistical basis. Areas for improvement include standardisation of sampling and follow-up, with precise record-keeping and consistent use of terminology and remission criteria.

The article has been peer-reviewed.

REFERENCES

1. Evang JA, Carlsen SM, Svartberg J et al. Endogent Cushings syndrom. Tidsskr Nor Laegeforen 2006; 126: 599–602. [PubMed]

2. Juszczak A, Morris D, Grossman A. Cushing's Syndrome. I: Feingold K, Ahmed SF, Anawalt B et al, red. Endotext. South Darthmouth, MA: MDText.com, 2024.

3. Fleseriu M, Auchus R, Bancos I et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol 2021; 9: 847–75. [PubMed][CrossRef]

4. Evang JA, Olsen AL. Cushings syndrom, primær utredning. Norsk Endokrinologisk Forening. https://metodebok.no/index.php?action=topic&item=8MpPRwfu Accessed 6.4.2025.

5. Newell-Price J, Morris DG, Drake WM et al. Optimal response criteria for the human CRH test in the differential diagnosis of ACTH-dependent Cushing's syndrome. J Clin Endocrinol Metab 2002; 87: 1640–5. [PubMed]

6. Hinojosa-Amaya JM, Cuevas-Ramos D. The definition of remission and recurrence of Cushing's disease. Best Pract Res Clin Endocrinol Metab 2021; 35. doi: 10.1016/j.beem.2021.101485. [PubMed][CrossRef]

7. Petersenn S, Beckers A, Ferone D et al. Therapy of endocrine disease: outcomes in patients with Cushing's disease undergoing transsphenoidal surgery: systematic review assessing criteria used to define remission and recurrence. Eur J Endocrinol 2015; 172: R227–39. [PubMed][CrossRef]

8. Statistisk sentralbyrå. Tabell 07459: Alders- og kjønnsfordeling i kommuner, fylker og hele landets befolkning (K) 1986 - 2025. https://www.ssb.no/statbank/table/07459/ Accessed 5.4.2025.

9. Stroud A, Dhaliwal P, Alvarado R et al. Outcomes of pituitary surgery for Cushing's disease: a systematic review and meta-analysis. Pituitary 2020; 23: 595–609. [PubMed][CrossRef]

10. Ramm-Pettersen J, Halvorsen H, Evang JA et al. Low immediate postoperative serum-cortisol nadir predicts the short-term, but not long-term, remission after pituitary surgery for Cushing's disease. BMC Endocr Disord 2015; 15: 62. [PubMed] [CrossRef]

11. Mehta GU, Ding D, Patibandla MR et al. Stereotactic Radiosurgery for Cushing Disease: Results of an International, Multicenter Study. J Clin Endocrinol Metab 2017; 102: 4284–91. [PubMed][CrossRef]

12. Jagannathan J, Sheehan JP, Pouratian N et al. Gamma Knife surgery for Cushing's disease. J Neurosurg 2007; 106: 980–7. [PubMed][CrossRef]

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