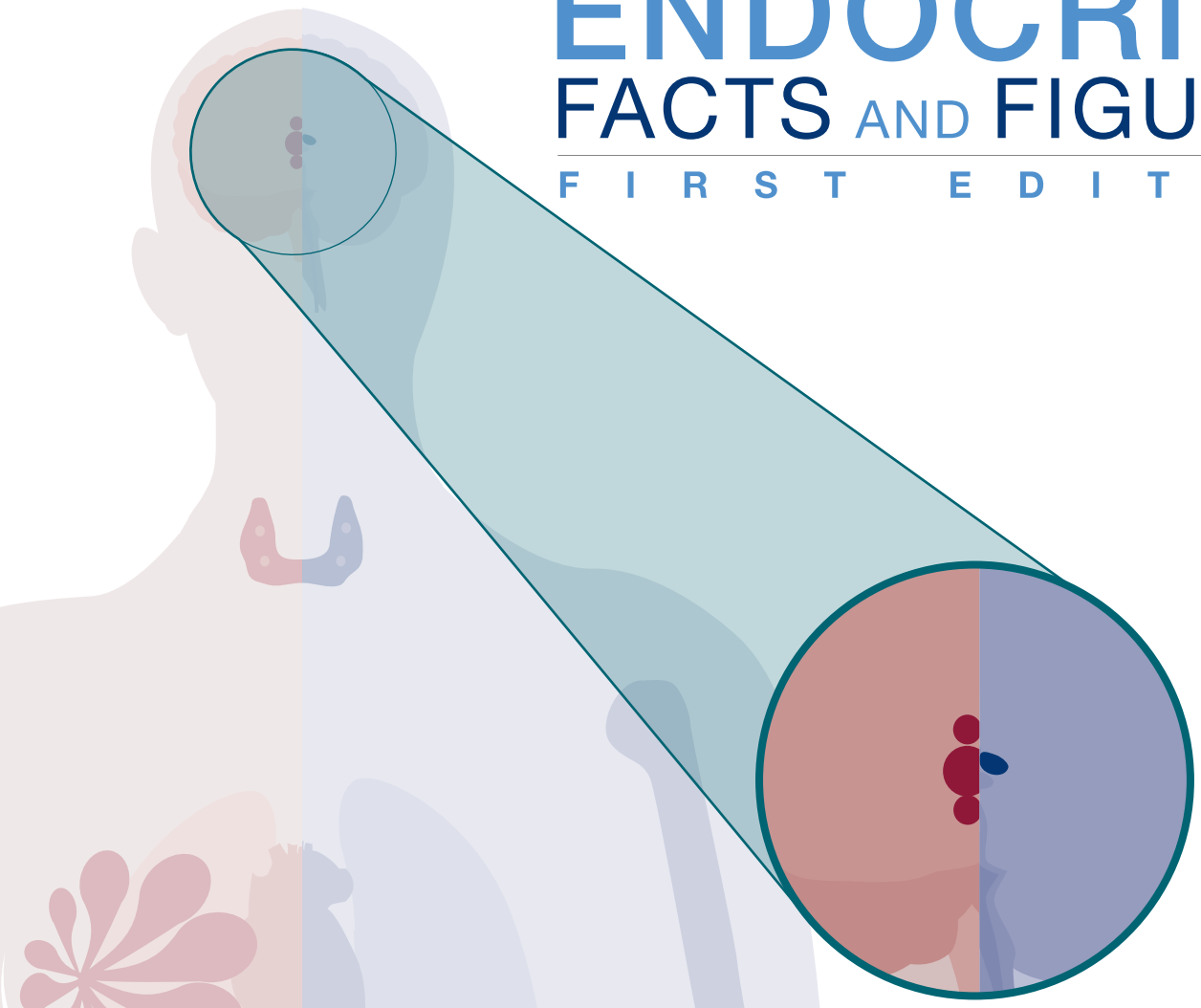
ENDOCRINE FACTS AND FIGURES

FIRST EDITION



HYPOTHALAMIC-PITUITARY

ENDOCRINE SOCIETY

COST BURDEN

$13,708

US ANNUAL COST OF **NON-FUNCTIONING PITUITARY ADENOMAS** PER PATIENT IN 2008[3]

$24,900

US AVERAGE ANNUAL COST OF **ACROMEGALY** PER PATIENT[4]

PREVALENCE

ACROMEGALY AFFECTS
78 AMERICANS PER MILLION PER YEAR

FOR EVERY **1,000,000 OLDER ADULTS** (≥65 YEARS)

>

FOR EVERY **1,000,000 CHILDREN** (0-17 YEARS)

HYPOPITUITARISM AFFECTS
<200,000 AMERICANS[2]

SEX DIFFERENCES

PROLACTINOMAS

10x

MORE COMMON IN FEMALES AGE 20-50 YEARS THAN MALES[5]

Source:

1 Burton, T.; Le Nestour E.; Neary, M.; Ludlam, WH. Incidence and prevalence of acromegaly in a large US health plan database. *Pituitary*. 2016.

2 Corenblum B. *Hypopituitarism*. 2011; http://emedicine.medscape.com/article/122287-overview#a0101. Accessed June 3, 2015.

3 Swearingen, B.; Wu, N.; Chen, S.Y.; Bulgar S.; Biller, B.M. Health care resource use and costs among patients with cushing disease. *Endocrine Practice*: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2011;17(5):681-690.

4 Broder, M.S.; Neary M.P.; Chang, E.; Cherepanov, D.; Katznelson, L. Treatments, complications, and healthcare utilization associated with acromegaly: a study in two large United States databases. *Pituitary*. 2014;17(4):333-341.

5 Casanueva, F.F.; Molitch, M.E.; Schlechte, J.A.; et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. *Clin Endocrinol* (Oxf). 2006;65(2):265-273.

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Mission Statement of the Endocrine Society

The mission of the Endocrine Society is to advance excellence in endocrinology and promote its essential and integrative role in scientific discovery, medical practice, and human health.

About Endocrine Facts and Figures

Endocrine Facts and Figures is a compendium of epidemiological data and trends related to a spectrum of endocrine diseases. The data is organized into nine chapters covering the breadth of endocrinology: Adrenal, Bone and Mineral, Cancers and Neoplasias, Cardiovascular and Lipids, Diabetes, Hypothalamic-Pituitary, Obesity, Thyroid, and Reproduction and Development.

All data is sourced from peer-reviewed publications, with an additional round of review by a group of world-renowned experts in the field. Additional oversight from the Endocrine Facts and Figures Advisory Panel ensured fair and balanced coverage of data across the therapeutic areas.

The first edition of **Endocrine Facts and Figures** emphasizes data on the United States. Future updates to the report will include additional data for other countries.

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For More Information

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Disclaimer

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HYPOTHALAMIC-PITUITARY

This chapter presents current epidemiological and trends data related to hypothalamic-pituitary disorders in the United States (US). Importantly, due to the rarity of most of these disorders, international-based studies are referenced to supplement sections where no US-based data were available.

The first section of this document focuses on pituitary dysfunction: anterior hypopituitarism/pituitary insufficiency, and posterior pituitary disease. The second section summarizes facts related to pituitary adenomas and other sellar lesions. Please note that Cushing's disease is covered in the Endocrine Facts and Figures: Adrenal chapter.

I PITUITARY DYSFUNCTION

1.1

HYPOPITUITARISM

Hypopituitarism, whether congenital or acquired, refers to the complete or partial deficit of anterior and/or posterior pituitary hormones.[1] While congenital hypopituitarism occurs due to the abnormal prenatal development of either the pituitary or hypothalamus, acquired hypopituitarism may occur either due to or as a response to the treatment of pituitary, non-pituitary, or hypothalamic tumors (i.e. surgery and radiation therapy); traumatic brain injury; subarachnoid hemorrhage; and autoimmune conditions.[2]

Prevalence and Incidence

Hypopituitarism is listed as a rare disorder by the National Institutes of Health. To date there are no US-based studies on the prevalence and incidence of hypopituitarism.

One published report indicated it affects less than 200,000 individuals in the US.[3] And the 2010 National Hospital Discharge Survey reported 17,101 US inpatient hospital visits with (panhypopituitarism/hypopituitarism) as one of any listed diagnoses, and 749 visits with this as the primary diagnosis. In addition, the reported average hospital stay was 5.4 days.[4]

Table 1 lists several European-based large-scale studies on prevalence and incidence of hypopituitarism.

Congenital hypopituitarism is a rare disease, with an estimated incidence of 1:3000 - 1:4000 births.[7] Mutations in genes encoding transcription factors and signaling molecules involved in hypothalamo-pituitary development are associated with the different etiologies of congenital hypopituitarism.[8-10] Table 2 summarizes the prevalence of the most common mutations among different populations.

Table 1

Prevalence of all-cause hypopituitarism.

POPULATION	DATA SOURCE	PREVALENCE PER 100,000	INCIDENCE PER 100,000	REFERENCE
Spain (n=146,000)*	Retrospective review of clinical data	45.5	4.21	Regal et al. 2001[5]
Spain (n=405,218)	Retrospective review of clinical data	37.5	2.07	Fernandez et al. 2013[6]

Note: *, in this cohort the causes of hypopituitarism were pituitary tumors (61%), non-pituitary lesions (9%), and non-tumor causes (30%, including idiopathic cases [11%]). In addition, approximately 50% of patients had three to five pituitary hormone deficiencies, with luteinizing hormone/follicle stimulating hormone being the most prevalent.

Table 2

Prevalence of genetic mutations associated to congenital hypopituitarism.

GENETIC MUTATION	POPULATION *	PREVALENCE (%)	REFERENCE
POU1F1	The Netherlands; (n=79)	1.2	De Graff et al. 2010[11]
LHX4	Japan;(n=71)	1.4	Dateki et al. 2010[12]
PROP1	International GENHYPOPIT network; (n=195)	13.3	Reynaud et al. 2006[13]

Note: *, in all studies, only patients with multiple pituitary hormone deficiency were studied. All studies included both children and adults.

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Acquired hypopituitarism may occur due to a variety of different reasons. Table 3 summarizes the prevalence of some of the most common causes of the disease.

Cost Burden

Although no data exist for US costs, in 2010, in Germany the annual cost of substitution therapy for patient with hypopituitarism after pituitary surgery in was US $1,576 per patients. In addition, under the assumption that 45.7% of pituitary surgeries result in hypopituitarism, the overall annual cost of lifelong therapy was estimated at $30.6 million.[20]

Demographic Differences

Most studies suggest that there are no significant sex differences in the prevalence of this disease (Table 4).

Life Expectancy and Mortality

Untreated hypopituitarism is associated with serious morbidity and premature mortality.[16,27,28] Several studies have shown that adults with hypopituitarism have increased mortality as compared to age- and sex-matched controls, with females having a higher standardized mortality ratio (SMR) than males (Table 5).[29,30]

In Spain, a 10-year follow-up study of 209 hypopituitary patients reported that 32 patients died during the study period, with the SMR being higher in males (8.92 vs. 7.34), and in younger patients (84.83 vs. 5.26). In addition, the diagnosis of acromegaly, previous radiotherapy, higher body mass index, diabetes mellitus, and cancer were associated with enhanced mortality. A lower survival rate was associated with older age at diagnosis, non-tumoral causes, previous radiotherapy, diabetes mellitus with poor metabolic control, and malignant disease.[6]

Aside from the all-cause mortality being higher in patients with hypopituitarism, specific-cause mortality is also increased in this population. Table 6 lists sex differences in specific-cause SMR.

Key Trends and Health Outcomes

Hypopituitarism can present itself as either subclinical or clinical, in which case the onset might be acute and severe.[32] Due to the diversity of possible pituitary hormone deficiencies that result from this disorder, diagnostic tests for hypopituitarism range from single measurements of baseline hormone levels to dynamic hormone testing. Moreover, since basal concentrations alone might not reflect pulsatile, circadian, or stimulus-specific secretion,

Table 3

Prevalence of acquired hypopituitarism.

CAUSE OF ACQUIRED HYPOPITUITARISM	DATA SOURCE	POPULATION	METHOD	PREVALENCE (%)	REFERENCE
Radiation therapy *	PubMed, EMBASE, Web of Science, CINAHL, Academic Search Premier and Cochrane Library	Studies on fractionated cranial radiotherapy for nasopharyngeal and intracerebral tumors, adults; (n=813)	Systematic review and meta-analysis of studies (1975-2009)	66	Appelman-Dijkstra et al. 2011[14]
Surgery	MEDLINE and EMBASE	Studies on transsphenoidal surgery for pituitary adenomas; (n=5,643)	Systematic review of studies (1990-2011)	Endoscopy: 8.51 (5.16-12.59); Microscopy: 11.64 (5.14-20.32)	Ammirati et al. 2013[15]
Traumatic brain injury	MEDLINE	Adults (n=941) and children (n=74)	Systematic review of studies (2000-2007)	27.5	Schneider et al. 2007[16]
Aneurysmal subarachnoid hemorrhage	MEDLINE	Adults (n=122)	Systematic review of studies (2000- 2007)	47	Schneider et al. 2007[16]

Note: *, the risk of acquired hypopituitarism from conventional radiation therapy versus stereotactic radiation therapy has been reported to be similar.[17-19]

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Table 4

Demographic characteristics of hypopituitarism adult cases.						
POPULATION	MALES (%)	AGE, YEARS	FOLLOW-UP DURATION, YEARS	PAN-HYPO-PITUITARISM, (%)	PARTIAL HYPO-PITUITARISM, (%)	REFERENCE
UK (n=172)	59.3	Median: 53M, 51F	N/A	31	69	Bates et al. 1996[21]
Sweden (n=344)	62.2	Mean: 52 (all M/F)	Median: 11.9	21.2	78.8	Bulow et al. 1997[22]
UK (n=1,014)	50.69	Median: 46.2 M, 45.3 F	Median: 12.1 M, 12.7 F	34.02	65.98	Tomlinson et al. 2001[23]
Sweden (n=1,411)	52.94	Mean: 56.9 (all M/F)	N/A	N/A	N/A	Svensson et al. 2004[24]
Netherlands (n=2,229)	52.0	Mean: 43.5 (all M/F)	Median: 6.1	N/A	N/A	Van Bundersen et al. 2011[25]
Global (n=13,983)	51.3	Mean: 43.8 (all M/F	Mean: 4.9	N/A	N/A	Gaillard et al. 2012[26]

Abbreviations: M, male; F, female; n, number; N/A, not available; UK, United Kingdom.

Table 5

Sex differences in all-cause mortality in patients with hypopituitarism.			
POPULATION	SMR		REFERENCE
	MALES	FEMALES	
International (n=5,412)	2.06	2.80	Nielsen et al. 2007[30]
UK (n=102)	1.50	2.29	Bates et al. 1996[21]
Sweden (n=3,214)	1.91	2.93	Bulow et al. 1997[22]
UK (n=514)	1.57	2.29	Tomlinson et al. 2001[23]
Sweden (n=747)	3.36	4.54	Svensson et al. 2004[24]
Netherlands (n=1,160)	1.06	1.66	Van Bundersen et al. 2011[25]
Global (n=7,174)	0.94	1.56	Gaillard et al. 2012[26]

Abbreviations: SMR, standardized mortality ratio; UK, United Kingdom.

Table 6

Specific-cause mortality in males and females with acquired hypopituitarism.					
TYPE OF MORTALITY	POPULATION	METHOD	SPECIFIC-CAUSE SMR		REFERENCE
			MALES	FEMALES	
Cardiovascular disease	Sweden (n=333)	Retrospective examination (1956-1987)	1.70	2.70	Rosen et al. 1990[31]
Cerebrovascular disease	Sweden (n=344)	Retrospective examination (1952-1992)	2.64	4.91	Bulow et al. 1997[22]
Respiratory disease	UK (n=1,014)	Patient follow-up (1992-2000)	2.10	3.41	Tomlinson et al. 2001[23]

Note: Studies included patients with different causes of hypopituitarism, including pituitary adenomas and craniopharyngiomas. Patients with acromegaly or Cushing's disease were excluded from analysis.

Abbreviation: SMR, standardized mortality ratio; UK, United Kingdom.

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dynamic testing may be required to further diagnosis, especially for assessment of adrenal and growth hormone reserve.[1,16,32]

Hypopituitarism may develop as a result of pituitary tumor treatment. For example, in the case of radiation therapy[2], reports indicate that 10 years after conventional fractionated irradiation, 50% of patients exhibit varying degrees of hypopituitarism.[33,34] Similarly, Gamma Knife surgery resection has been associated with an increased risk of developing hypopituitarism.[35]

In addition, hypopituitarism may develop after pituitary surgery, depending on factors such as tumor size, degree of infiltration, and surgeon experience.[2] For example, one study reported that 0, 7.2, and 13.6% of patients with tumor diameters of <20, 20-29, and ≥30 mm, respectively, developed new hypopituitarism after endonasal transsphenoidal adenoma removal.[36] Resolution of the disorder has been related to younger age (39 vs. 52 years), and absence of intraoperative cerebrospinal fluid leak.[36] Additional factors associated with a higher recovery of post-operative pituitary function include no tumor rests on post-operative pituitary imaging, and no pathological evidence of an invasive nature.[37]

In terms of the specific types of post-operative hormone deficiencies, Webb and colleagues reported that in 234 patients with pituitary adenomas, 52 patients developed new post-operative pituitary hypofunction: 27% ACTH deficiency, 14.5% growth hormone (GH) deficiency, 10.5% thyroid-stimulating hormone deficiency, 16.5% gonadotropin deficiency, and 13% prolactin deficiency.[37] Importantly, approximately 50% of patients recover at least one of the pituitary hormone deficiencies caused by surgery during the immediate post-operative stage.[37,38]

In the particular case of GH deficiency, it has been shown that adults with primary hypothalamic-pituitary diseases before and after any medical intervention (defined as neurosurgery, radiotherapy and medical therapy) are at greater than 80% risk of severe GH deficiency.[39] Moreover, a study in Denmark reported that GH deficiency increased mortality in both genders, when compared with controls.[40] The Endocrine Society 2011 Clinical Practice Guideline for the Evaluation and Treatment of Adult Growth Hormone Deficiency provides detailed recommendations for the diagnosis and management of this type of pituitary deficiency.[2]

Overall, adequate hormone replacement can improve quality of life, morbidity, and mortality associated with hypopituitarism.[32] Table 7 summarizes health outcomes data for adrenocorticotropic and GH deficiencies.

Importantly, hypopituitarism may present a number of comorbidities including, dyslipidemia, cardiovascular complications, and osteoporosis. Thus, treating hypopituitarism, in addition to pituitary hormone substitution, may include managing comorbidities.[32]

1.2 POSTERIOR PITUITARY DISEASE

1.2.1 Central Diabetes Insipidus

Central diabetes insipidus (CDI) is a disease in which large volumes of dilute urine (polyuria) are excreted due to deficiency of arginine vasopressin (AVP), also called antidiuretic hormone (ADH). Known causes of CDI include mass lesions such as germinomas and craniopharyngiomas, infiltrative disease such as Langerhans cell histiocytosis and sarcoidosis, trauma resulting from surgery or an accident, neoplastic metastases, and midline cerebral and cranial malformations. In rare cases, the underlying cause can be genetic defects in AVP synthesis.[43] In addition, roughly one quarter of adult cases and half childhood cases are considered idiopathic.[44,45]

CDI may present as either transient or permanent. Due to the inability to concentrate urine, patients with CDI may develop dehydration and metabolic abnormalities, including hypernatremia, that can be life threatening if not recognized and treated in a timely manner with AVP or the AVP analog, desmopressin, and appropriate fluids.[46]

Prevalence and Incidence

Data on the epidemiology of CDI are limited. A 2007-2011 study using linked data from the Danish National Prescription Registry, and Danish National Patient Registry identified 1,285 patients with CDI during the 5-year period of the study. The average overall 5-year prevalence of CDI was estimated to be 23 patients per 100,000 inhabitants. The average annual incidence was reported to be three to four new cases per 100,000 inhabitants.[47]

CDI is a common complication of pituitary surgery. The reported incidence of post-surgical CDI ranges between 1

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to 67%, most likely due to inconsistencies in the definition of CDI across the literature.[46] Post-surgical CDI can be transient or permanent, further complicating the definition. Traumatic brain injury and subarachnoid hemorrhage can also result in CDI. Table 8 summarizes available data on the prevalence and incidence of CDI by cause.

One study reported that gestational CDI has a prevalence of up to 1 in 30,000 pregnancies, and may be due to a variety of causes that predate pregnancy or start during gestation.[52]

Because the placenta produces vasopressinase, an enzyme that degrades vasopressin, pregnancy may make manifest previously undiagnosed subclinical CDI. Furthermore, since polyuria is often considered normal during pregnancy, clinicians caring for pregnant women are recommended to consider screening for gestational CDI (along with gestational diabetes mellitus) in those who develop polyuria and polydipsia, as it could be associated with serious underlying pathology.[53]

Demographic Differences

Studies have reported that CDI is more prevalent in children and older adults (>80 years of age).[47] Primary tumors of the pituitary fossa result in CDI in 50% of children and 30% of adults, while head trauma to the posterior pituitary gland accounts for 2% of cases in children and 17% in adults.[54] Table 9 illustrates the age-specific prevalence of CDI in Denmark.

Among adults, 9% of CDI results from inadvertent neurosurgical damage to the posterior pituitary gland, 8% from metastatic carcinoma, and 6% from intracranial

Table 7

Effects of hormone substitution therapies on hypopituitarism.

HORMONE DEFICIENCY	THERAPEUTIC APPROACH	DATA SOURCE	OUTCOME	REFERENCE
ACTH	Once-daily oral hydrocortisone dual-release tablet *	Germany; multicenter clinical trial and university hospital centers (n=64)	Sustained serum cortisol profile, reduced weight, blood pressure and improved glucose metabolism versus 3 times/day conventional hydrocortisone tablets.	Johannson et al. 2012[41]
GH	GH therapy	Endocrine Society Clinical Practice Guideline. Review of studies	Benefits in body composition, bone health, cardiovascular risk, and quality of life.	Molitch et al. 2011[2]
		11 countries; The Hypopituitary Control and Complications Study, 2000, adult onset (n=1,123)	After 3 years on GH-therapy, serum cholesterol and body fat percentage decreased in females (-0.31 ± 1.04 mmol/liter; -3.07 ± 7.77) and males (-0.40 ± 1.04 mmol/liter; -2.84 ± 6.76)	Attanasio et al. 2002[42]
		Sweden; retrospective analysis of adults without GH therapy, 1987-1992 (n=1,411) versus prospective study of GH-treated patients, 1990-2000 (n=289)	Overall mortality: without GH (RR, 3.8) > GH-treated (RR, 0.84)	Svensson et al. 2004[24]

Abbreviations: ACTH, adrenocorticotropic hormone; GH, growth hormone; RR, risk ratio.

Note: *, this preparation is not available in the US. In the US, hydrocortisone is generally given in 2 or 3 doses over the course of the day; the usual total daily dose is 15-20 mg/day and rarely exceeds 30 mg/day.

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hemorrhage and hypoxia. A post-infectious disease process and histiocytosis X cause CDI in 2% and 16% of children, respectively.[54]

No data on ethnic/racial differences in the epidemiology of CDI are available.

Life Expectancy and Mortality

In a prospective study of all patients admitted to the surgical ICU of a level I trauma center with severe head injury (n=436), CDI occurred in 15.4% of all patients and it was identified as an independent risk factor for death.[55]

Key Trends and Health Outcomes

In general, the diagnostic standard for CDI is a water deprivation test with an assessment of AVP activity; however, test interpretation and AVP measurement are often challenging.[56]

Recent data on a newly available assay for copeptin, the C terminus of the AVP precursor, provide promise for a higher diagnostic specificity and simplification of the differential diagnostic protocol for CDI; however, this assay is not yet readily available commercially.[56]

Importantly, since CDI may be the end result of a number of conditions that affect the hypothalamic-neurohypophyseal system, patients should undergo further diagnostic testing aimed to identify the underlying cause of the disorder. Because such conditions may also affect the anterior pituitary, an evaluation of anterior pituitary function is also usually indicated.[43]

Desmopressin acetate is the synthetic analog of AVP and has been used for treating CDI for over 40 years, in a variety of formulations: intranasal solution, injectable solution, conventional tablets, and tablets that dissolve in the mouth.[57,58]

Table 8

Prevalence of central diabetes insipidus by cause.

CAUSE	DATA SOURCE	POPULATION	PREVALENCE		REFERENCE
			TEMPORARY CDI	PERMANENT CDI	
Transsphenoidal pituitary adenoma surgery	Medical records, Stanford University School of Medicine	US (n=857)	18.3%	2.0%	Nemergut et al. 2005[48]
Transsphenoidal pituitary adenoma surgery	Medical records University of Bonn, Germany	Germany (n=57)	38.5%	8.7%	Kristof et al. 2009[49]
Transsphenoidal pituitary adenoma surgery	Systematic review of international studies (1990-2011)	International (n=5,643)	10.23%	4.25%	Ammirati et al. 2013[15]
Endoscopic transsphenoidal surgery of sellar and parasellar lesions	Detroit Medical Center, department of neurosurgery records (2006-2011)	US (n=172)	8.7%	8.1%	Schreckinger et al. 2013[46] *
Traumatic brain injury **	Beaumont Hospital head trauma database; Dublin	Ireland; age 15-65 years, (n=102)	21.6%	6.9%	Agha et al. 2004[50]
Subarachnoid hemorrhage (SAH) ***	Medical records from clinical centers	Italy; age 51.9±2.2 years; (n=32)	6.25%	2.8%	Aimeretti et al. 2005[51]

Abbreviations: CDI, central diabetes insipidus; US, United States.

Notes: *, Tumor volume and histopathology (Rathke's cleft cyst and craniopharyngioma) are significant predictors of post-surgical CDI. Significant indicators of development of the disorder were postoperative serum sodium, preoperative to postoperative change in sodium level, and urine output prior to administration of desmopressin (an increase in serum sodium of ≥2.5 mmol/L is a positive marker of development of DI with 80% specificity, and a postoperative serum sodium of ≥145 mmol/L is a positive indicator with 98% specificity). ** CDI was diagnosed as plasma sodium > 145 mmol/liter in presence of polyuria of > 3.5 liter per 24 hours and dilute urine (osmolality < 300 mOsm/kg); ***, DI was diagnosed by massive dilute urine volume (> 2.5-3 liter per 24 hour) with low urine osmolality (< 300 mOsm/kg).

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1.2.2

Hyponatremia

Hyponatremia is an electrolyte disorder. Serum sodium concentrations < 125 mmol/L are considered an indication of severe hyponatremia, and serum levels < 115 mmol/L are associated with substantial morbidity and increased mortality.[59,60]

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of hyponatremia.[61] It's caused by excess of renal water reabsorption due to inappropriate antidiuretic hormone (vasopressin) secretion.[62] Sherlock et al. reported that 62% of cases of hyponatremia resulted from SIADH.[63]

Prevalence and Incidence

Hyponatremia is the most common electrolyte disorder encountered in hospital inpatients and clinical practice.[61,64] Data from NHANES 1999-2004 (n=14,697) showed that the prevalence of US adults (age ≥ 18 years) with hyponatremia (serum sodium < 133-145 mmol/L for years 1999-2002, and <136-144 mmol/L for years 2003-2004) was 1.72%. Table 10 lists the prevalence of hyponatremia by cause.

Table 9

5-year prevalence of central diabetes insipidus in Denmark per age group, 2007-2011.	
AGE	PREVALENCE (PER 100,000 INHABITANTS)
0 – 9 years	43.6
10 – 19 years	34.0
20 – 29 years	9.7
30 – 39 years	11.8
40 – 49 years	16.9
50 – 59 years	19.0
60 – 69 years	22.5
70 – 79 years	26.3
80 – 89 years	35.6
90+ years	34.5
	Source: Juul et al. 2014[47]

Demographic Differences

Data from NHANES indicated hyponatremia was more common in females as opposed to males (2.1% vs. 1.3%), and patients with hyponatremia were significantly older (52.8 vs. 45 years). Overall, hyponatremia was more common in subjects with comorbidities than those with none (2.3% vs. 1.04%); specifically, hyponatremia was significantly higher among patients with hypertension, diabetes, coronary artery disease, cancer, stroke, chronic obstructive pulmonary disease, and psychiatric disorders.[65]

Life Expectancy and Mortality

Hyponatremia is associated with greatly increased morbidity and mortality,[61] and if not treated appropriately may lead to death.[64] Untreated acute hyponatremia can cause substantial morbidity and mortality as a result of osmotically induced cerebral edema, and excessively rapid correction of chronic hyponatremia can cause severe neurologic impairment and death as a result of osmotic demyelination, particularly of the pons.[66]

Hyponatremia, which can be profoundly symptomatic, has also been linked to longer hospital stays, admission to the ICU, and costly readmissions.[63,67-70] A recent analysis of NHANES data reported the overall mortality rate over the period 1999-2006 at 11% for hyponatremic subjects versus 4% for their normal counterparts. In addition, among subjects with hyponatremia, mortality rates were

Table 10

Hyponatremia by cause.			
POPULATION	STUDY DESIGN	CAUSE	PREVALENCE (%)
Ireland (n=1,698) patients with hyponatremia	Retrospective analysis of hospital data	Pituitary disorders	6.25
		Traumatic brain injury	9.60
		Intracranial neoplasm	15.8
		Subarachnoid hemorrhage	19.6
		Spinal disorders	0.81
	Source: Sherlock et al. 2009[63]		

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not affected by sex or race/ethnicity.[65] Table 11 presents data on factors that have been shown to significantly increase mortality rate among hyponatremic patients.

Key Trends and Health Outcomes

According to recently published expert panel recommendations on the diagnosis, evaluation, and treatment of hyponatremia, in cases where there is a remote possibility that the primary diagnosis is SIADH and either significant central nervous system symptoms from hyponatremia are present or the starting serum [Na] is 120 mmol/L, hypertonic saline (e.g., 3% NaCl) should be used for the initial diagnostic volume challenge to avoid any risk of lowering the serum [Na] further.[71]

Initial treatment consists of withholding all diuretics and cautiously repleting the patient with isotonic fluid if central nervous system abnormalities are mild. Clinicians should use hypertonic saline to raise the serum [Na] by 4-8 mmol/L acutely when seizures or a significantly altered level of consciousness are present. However, they should not use furosemide with the hypertonic saline because of the risk of precipitating hypotension, and clinicians should administer a minimum of hypertonic fluid in anticipation of the water diuresis that will ensue.[71]

The Food and Drug Administration has approved vasopressin receptor antagonists for the management of hyponatremic disorders. However, proper and effective use of these and other therapies requires careful thought and guidance.[71]

II PITUITARY ADENOMAS AND OTHER SELLAR LESIONS

Pituitary adenomas are a diverse group of tumors arising from the pituitary gland. The most common health issues associated with these lesions are an increase/decrease of pituitary hormone secretion and/or loss of visual

Table 11

All-cause mortality among hyponatremic patients.

DATA SOURCE	POPULATION	FACTOR		MORTALITY RATE (%)
NHANES 1999-2004 (followed-up 2006)	US (n=14,679)	Sex	Males	13
			Females	9.8
		Race/ethnicity	Non-Hispanic whites	12
			Non-Hispanic blacks	8.6
			Hispanic	6.7
		Body mass index *	Normal weight	17
			Obese	0.2
		Poverty income ratio *	0-0.99	19
			≥ 5	1.6
		Comorbidities *	No comorbidities	2.5
			Coronary artery disease	30
			Congestive heart failure	38
			Liver disease	37
			Kidney disease	32
			Cancer	25

Source: Mohan et al. 2013[65]

Abbreviations: US, United States.

Note: *, factors showing a statistically significant increase in mortality rate ($p<0.001$).

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field (mostly due to large tumors that compress parts of the brain that control visual function).[72] Other common issues include headache, amenorrhea, loss of libido, and lethargy.[72] Standard incidence rates have increased significantly and there are now 5.8/100,000 new cases per year.[73]

This section presents data on functioning adenomas, which secrete hormones and disrupt normal homeostasis and function resulting in disease, such as acromegaly (excess GH), hyperprolactinemia (excess prolactin), and hyperthyroidism (excess thyroid stimulating hormone). This section also presents data on non-functioning adenomas and non-adenomatous sellar lesions, (e.g., neoplastic, and infiltrative lesions).

Table 12 summarizes data on the overall prevalence of pituitary adenomas.

2.1 FUNCTIONING ADENOMAS

Conditions associated with functioning pituitary adenomas include acromegaly, hyperprolatinoma, and thyrotropin (TSH)-secreting adenomas (TSHomas).

2.1.1 Acromegaly

Acromegaly is characterized by excess GH secretion and insulin-like growth factor 1 (IGF-1) concentrations, most commonly due to a pituitary adenoma.

Prevalence

Table 13 summarizes data on the prevalence of acromegaly.

Cost Burden

The economic burden of acromegaly in the US is largely unknown. One study, however, examined the associated healthcare costs of acromegaly in the US from data from claims databases between 2002 and 2009 for 2,171 acromegaly patients. In this study, results indicated that acromegaly has a mean healthcare cost of $24,900 per patient per year, with medical costs accounting for $17,715, and $7,185 accounting for pharmacy costs.

Table 12

Overall prevalence of pituitary adenomas.			
POPULATION	DATABASE	PREVALENCE PER 100,000	REFERENCE
UK (n=81,149)	Sixteen general practitioner surgeries covering the area of Banbury.	77.6	Fernandez et al. 2010[74]
Belgium; (n=71,972)	Specialist and general medical practitioner patient populations, referral hospitals, and investigational centers	94	Daly et al. 2006[75]

Abbreviations: n, number; UK, United Kingdom.

Table 13

Prevalence of acromegaly.			
POPULATION	DATA SOURCE	PREVALENCE PER 100,000	REFERENCE
US (n=123 million)	Administrative claims data	7.8 *	Burton et al. 2016[76]
Mexico (n=442)	The Acromegaly Clinic at Hospital de Especialidades in Mexico City	2.94	Mercado et al. 2014[77]
UK (n=81,149)	Sixteen general practitioner surgeries covering the area of Banbury.	8.6	Fernandez et al. 2010[74]
UK (n=501)	West Midlands Acromegaly Database	8.78	Sherlock et al. 2009[69]

Abbreviations: US, United States; UK, United Kingdom.

Note: * Prevalence estimates increased with age, ranging from 29-37 cases per million among children aged 0-17 years old to 148-182 cases per million among adults aged 65 years and older. Males and females were similarly affected; each with approximately 77 cases per million each year.

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Importantly, medical costs were primarily associated with non-emergency department outpatient services ($12,268), and inpatient hospitalization ($5,213).[78]

In addition, the presence of any complication statistically increased annual costs. In unadjusted comparisons to patients without complications, total costs were increased by $18,840 in patients with cardiovascular abnormalities, $16,701 in those with sleep apnea, $14,225 in those with colon neoplasms, %10,989 in those with musculoskeletal abnormalities, and $9,906 in those with hypopituitarism. Interestingly, costs were $2,610 lower in acromegaly patients with reproductive abnormalities than in those without. After adjusting for differences in age, gender, region, and cardiovascular risk factors, costs were increased by $8,401 in patients with colon polyps or colon cancer, by $7,502 in patients with musculoskeletal abnormalities, by $13,331 in those with cardiovascular abnormalities, by $10,453 in those with sleep apnea, and by $6,742 in those with hypopituitarism.[78]

Life Expectancy and Mortality

Table 14 presents mortality data on patients with acromegaly.

Key Trends and Health Outcomes

A recent study by Nachtigall et al. that included 100 patients at a neuroendocrine clinical center reported that primary care doctors play the major role in diagnosis of acromegaly, and that while 18% of patients present no symptoms at the time of diagnosis, acral changes (24%), and headaches (20%) are the most prevalent presenting symptoms prompting diagnosis.[79]

Due to the variable nature of the disorder, an individualized treatment is necessary. However, the Endocrine Society 2014 Clinical Practice Guideline for Acromegaly provides evidence-based recommendations for the evaluation and management of acromegaly, including an algorithm for an integrated multidisciplinary therapeutic approach.[80]

Overall, the Endocrine Society Acromegaly Task Force suggests the following goals of management: 1) a biochemical target goal of an age-normalized serum IGF-1 value, 2) using a random GH < 1.0 ug/L as a therapeutic goal, and 3) maintaining the same GH and IGF-1 assay in the same patient throughout management.[80]

In terms of treatment strategies, the Task Force recommends transsphenoidal surgery as the primary therapy in most patients. However, in patients with parasellar disease making total resection unlikely, surgical debulking is suggested to improve subsequent response to medical therapy. Finally, medical therapy is recommended for patients with persistent disease following surgery, while radiation therapy is suggested in cases of residual tumor mass following surgery, or in cases where medical therapy is unavailable, unsuccessful, or not tolerated. For more detailed information please refer to the Endocrine Society 2014 Clinical Practice Guideline for Acromegaly.[80]

Recently, Broder et al. reported that out of 2,171 acromegaly patients, 77.8% received the majority of their care from non-endocrinologists, and 30.8% used pharmacologic treatment.78 Table 15 summarizes the monitoring tests and treatments used by these patients during the 12-month study period.

Table 14

Mortality in patients with acromegaly.

POPULATION	DATA SOURCE	TYPE OF MORTALITY	SMR OVERALL	REFERENCE
UK (n=501)	West Midlands Acromegaly Database	Overall	1.7	Sherlock et al. 2009[69]
		Prior radiotherapy	2.1	
		Prior ACTH deficiency	2.5	
		Prior gonadatropial deficiency	2.1	
Mexico (n=442)	The Acromegaly Clinic at Hospital de Especialidades in Mexico City	Overall	0.72	Mercado et al. 2014[77]
		Last GH above/below 2.5 ng/mL	1.5/0.44	
		Last GH above/below 1 ng/mL	1.17/0.16	
		Last IGF-1 above/below 1.2 times the upper limit of normal	0.94/0.46	

Abbreviations: SMR, standardized mortality rate; n, number; US, United States; UK, United Kingdom.

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In terms of complications related to acromegaly, the most common are musculoskeletal abnormalities (25.6%), hypopituitarism (16.6%), sleep apnea (11.5%), cardiovascular abnormalities (10.3%), reproductive system abnormalities (9.3%), and colon neoplasms (6.6%). In addition, cardiovascular risk factors have been reported in 47.6% of patients: hypertension (31%), hypertriglyceridemia (19.8%), and diabetes (17.5%). When conducting unadjusted comparisons, inpatient hospitalizations increased in patients presenting any complication, except in the case of reproductive abnormalities, which were related to a decrease in hospitalization. Similarly, in comparison to patients without complications, emergency department visits were more common in patients with cardiovascular disease, musculoskeletal conditions, and hypopituitarism. After adjusting for differences in age, gender, region, and cardiovascular risk factors, musculoskeletal abnormalities increased the odds of hospitalization (odds ratio [OR]: 1.76), as did cardiovascular abnormalities (OR: 2.93), and sleep apnea (OR: 1.56). Further, the odds of an emergency department visit increased with musculoskeletal (OR: 1.87), and cardiovascular abnormalities (OR: 2.32).[78]

2.1.2

Prolactinomas

Prolactinomas are usually small and rarely grow, but some can become very large.[81] They are an important cause of hypogonadism and infertility.[82] Prolactinomas, while benign, secrete prolactin and can result in a condition called hyperprolactinemia, a higher than normal level of prolactin in the blood.[81]

Hyperprolactinemia may result in hypogonadism, infertility, and galactorrhea, or it may remain asymptomatic.[82-84] Bone loss occurs secondary to hyperprolactinemia-mediated sex steroid attenuation. Spinal bone density is decreased by approximately 25% in women with hyperprolactinemia and is not necessarily restored with normalization of prolactin levels.[85]

Prevalence

The most common type of pituitary adenomas are prolactinomas.[86] Prolactinomas account for approximately 40% of all pituitary adenomas.[82] Table 16 lists the prevalence of prolactinomas.

Table 15

Test and treatments for acromegaly used during a 12-month study period.

POPULATION	TEST OR TREATMENT	PERCENTAGE (%)
2,171 acromegaly patients (mean age: 45.3 years; 49.7% female)	Biochemical monitoring tests	56
	IGF-1	53.7
	GH	31.7
	Acromegaly treatment	
	Surgery	5.3
	Radiation	2.3
	Pharmacological treatment	30.8
	Octreotide long-acting release	18.6
	Dopamine agonists	9.8
	Octreotide short-acting	4.7
	Pegvisomant	4.1
	Lanreotide	1.2

Source: Broder et al. 2014[78]

Abbreviations: IGF-1, insulin-like growth factor-1; GH, growth hormone.

Note: individual patients could have more than one type of test or treatment. For example, of patients receiving pharmacological therapy, 78% used only one treatment, 19.3% used two, 2.5% used three, and 0.1% used 4 types of treatment during the study year. In the case of monitoring tests, 56% of patients has at least 1 IGF-1 or GH test, 53.7% had ≥ 1 IGF-1, and 31.7% had ≥ GH test.

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Demographic Differences
Prolactinomas occur in both sexes, but are more common in women.[81] These tumors occur most frequently in females aged 20-50 years old, at which time the female-to-male ratio is approximately 10:1. In the pediatric-adolescent age group, prolactinomas have a prevalence of 100/million population, and account for less than 2% of all intracranial tumors. [81]

Prolactinomas occur in approximately 30% of patients with multiple endocrine neoplasia type 1, and in this setting they may be more aggressive than their sporadic counterparts. Few studies report familial cases of prolactinoma unrelated to multiple endocrine neoplasia type 1 (known as Familial Isolate Pituitary Adenoma Syndrome).[86]

Key Trends and Health Outcomes
The ultimate goals of therapy for prolactinomas are reversal of hypogonadism through the normalization of hyperprolactinemia and control of the tumor mass. Medical therapy with dopamine agonists is highly effective in the majority of cases and represents the mainstay of therapy. There has been a long-held belief that medical therapy is a lifelong requirement; however, a subset of patients has achieved successful withdrawal from dopamine agonists. Complicated situations, such as resistance to dopamine agonists, pregnancy, and giant or malignant prolactinomas, may require multimodal therapy involving surgery, radiotherapy, or both.[82,87]

Studies have reported the reversal of hypogonadism in 44-62% of cases, usually within 6 months after starting treatment with dopamine agonists.[88,89] Furthermore, a study reported the recovery of other hormonal axes following adenoma shrinkage.[90] Hormonal re-evaluation should be performed to avoid unnecessary life-long hormone replacement.

Table 17 summarizes treatment outcomes associated with different therapeutic approaches.

2.1.3
Thyrotropin-Secreting Adenomas (TSHomas)

An excess of TSH has been reported in 0.5-3% of pituitary tumors and can result in hyperthyroidism.[92] In this type of central hyperthyroidism the TSH secretion from the pituitary tumor drives the hyperthyroidism and therefore the TSH is high or inappropriately normal in the setting of hyperthyroxinemia, and signs and symptoms of hyperthyroidism are typically present.[92,93]

Prevalence
TSHomas account for 1 percent of all pituitary adenomas.[94] Table 18 lists the age-standardized national prevalence and incidence of TSHomas.

Life Expectancy and Mortality
A study by Sughrue et al. concluded there were not enough data to formulate an accurate SMR for TSHomas.[96] Table 19 lists the treatment options for TSHomas.

Key Trends and Health Outcomes
Table 19 summarizes key therapeutic strategies for the treatment of TSHomas.

2.2
NON-FUNCTIONING ADENOMAS AND NON-ADENOMATOUS SELLAR LESIONS

A non-functioning pituitary adenoma is a pituitary adenoma that is not hormonally active (in other words, not associated with clinical syndromes such as amenorrhea-galactorrhea in the context of prolactinomas, acromegaly, Cushing's disease, or hyperthyroidism secondary

Table 16

Prevalence of prolactinomas.

POPULATION	DATA SOURCE	PREVALENCE PER 100,000	REFERENCE
Belgium (n=71,972)	Specialist/general practitioner patient populations, referral hospitals, research centers	62.4	Daly et al. 2006[75]
United Kingdom (n=81,149)	Sixteen general practitioner surgeries covering the area of Banbury.	44.2	Fernandez et al. 2010[74]

Abbreviations: UK, United Kingdom; n, number.

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Table 17

Treatment outcomes of hyperprolactinemia.				
POPULATION	DATA SOURCE	TREATMENT	OUTCOME	REFERENCE
Italy, (n=41 males with macroprolactinoma (age 17-70 yr) (n= 10 males with microprolactinoma (age 18-53 yr).	Prospective analysis of clinical data	24 months of cabergoline treatment	75.6% patients with macroprolactinoma and 80% with microprolactinoma achieved normal prolactin levels	Colao et al. 2004[88]
International cohort (n=3,000)	Eight randomized and 178 non-randomized studies	Dopamine agonists	A median of 68% achieved normalization of prolactin levels	Wang et al. 2012[91]
International cohort (n=2,137 microadenomas; 2,226 macroadenomas)	Data from 50 published papers on surgical resection	Surgical resection	74.7% of microadenomas and 33.9% of macroadenomas achieved normalized PRL levels	Gillam et al. 2006[82]

Abbreviations: SMR, standardized mortality rate; CVR, cardiac valve regurgitation; yr, year; n, number.

Table 18

Prevalence of thyrotropin-secreting adenomas (TSHomas).				
POPULATION	DATABASE	PREVALENCE	INCIDENCE	REFERENCE
Hospital database Swedish university medical centers; (n= 9.2 million)	The Swedish Pituitary Registry and World Health Organization coding data	0.28 per 100,000	0.05 per 1 million (1990-1994) 0.26 per 1 million (2005-2009)	Onnestam et al. 2013[95]

Abbreviations: n, number

Table 19

Treatment options for thyrotropin-secreting adenomas (TSHomas).				
POPULATION	DATA SOURCE	TREATMENT	OUTCOME	REFERENCE
Sweden (n=28)	All Swedish university medical centers	Most patients (n = 22) underwent pituitary surgery, five had radiotherapy, and six had somatostatin analogues	18 patients were cured; 25% remained uncontrolled. Subjects treated for putative primary hyperthyroidism prior to diagnosis had TSH levels more than double those with intact thyroid at diagnosis.	Onnestam et al. 2013[95]
Italy (n=70)	Two tertiary referral centers in Milan, Italy	97% of patients were treated with surgery; in 27% of them radiotherapy was associated.	75% of patients normalized thyroid function, 58% normalized both pituitary imaging and hormonal profile, 9% developed pituitary deficiencies, and 3% had tumor or hormonal recurrence, all within the first 2 years after surgery. At last follow-up, 80% of patients normalized thyroid function, whereas 20% were currently on medical treatment.	Malchiodi et al. 2014[97]

Abbreviations; TSH, thyrotropin

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to TSHomas). They account for 15-30% of pituitary adenomas.[98]

2.2.1
NEOPLASTIC

2.2.1.1
Non-functioining Adenomas

Prevalence

Valassi et al. analyzed the records of 1,469 transsphenoidal procedures performed between 1998 and 2009 and reported that 116 (7.9%) were not pituitary adenomas.106 Of these 116 patients (45 men, 71 women; mean age 45 years), 53% had cystic lesions, 22% benign neoplasms, 16% malignancies, and 9% inflammatory lesions.[106]

In addition, Rathke's cysts, the most common lesions, represented 42% of all cases. Twenty-five per cent of malignant lesions were metastases, and some of the malignancies (e.g., fibrosarcoma, lung metastasis) had a radiographical appearance suggestive of a pituitary adenoma.[106]

The most common presenting symptoms associated with nonadenomatous lesions were visual field impairment (51%) and headache (34%). Pre-operative pituitary dysfunction was present in 58% of cases, with hyperprolactinemia (35%), hypogonadism (23%), and adrenal insufficiency (23%) found most frequently.[106]

Postoperative resolution of headache and visual symptoms occurred in 63% and 65% of patients, respectively. Of 64 preoperative endocrine abnormalities, 23 had recovered after surgery (34%). Of these 23, 17 were cases of hyperprolactinemia (77%), three of hypogonadism (14%), two of central hypothyroidism (9%) and one of hypocortisolism. Twelve new cases of endocrine dysfunction occurred after surgery (12/116; 10%).[106]

Table 20 presents data on the prevalence of non-functioning adenomas.

Cost Burden

A retrospective cohort study that examined insurance claims databases reported that in 2008, the annual cost of treating clinically non-functioning adenomas was $13,708 per patient in the US.[101]

Life Expectancy and Mortality

A very large Swedish registry study of patients with non-functioning pituitary adenomas showed an overall excess mortality in women and in patients with a young age at diagnosis. Increased mortality was seen for cerebrovascular and infectious diseases.[100]

A study in the United Kingdom reported that only age at diagnosis remained an independent predictor of mortality (hazard ratio 1.10; 95% CI, 1.07-1.13, p<0.001), whereas sex, presentation with acute apoplexy, extent of tumor removal, radiotherapy, recurrence, untreated GH deficiency, follicle-stimulating hormone/luteinizing hormone deficiency, ACTH deficiency, TSH deficiency, and treatment with desmopressin for CDI had no impact.[102] Tables 21 summarizes data on life expectancy and mortality of patients with non-functioning adenomas.

Key Trends and Health Outcomes

Table 22 presents data on key trends and health outcomes related to the treatment of non-functioning adenomas.

2.2.1.2
Craniopharyngiomas

Prevalence

Table 23 summarizes available data on the prevalence of craniopharyngiomas and nonadenomatous sellar lesions.

Life Expectancy and Mortality

One retrospective study conducted in the United Kingdom reported that patients with after surgery for craniopharyngiomas had an SMR 8.75 (95% CI of 5.4-13.3). For women, the SMR was 10.51 (95% CI 5.04-19.3) and for men it was 7.55 (95% CI 3.77-13.52). The study concluded that patients with craniopharyngiomas had high rates of mortality and morbidity, yet the underlying causes for these mortality rates remain poorly understood.[109]

Key Trends and Health Outcomes

Pediatric patients with sellar masses such as craniopharyngioma or cyst of Rathke's pouch frequently suffer disease- and treatment-related sequelae.[110]

A study by Daubenbuchel et al. of 177 pediatric patients (163 craniopharyngioma and 14 Rathke's pouch) concluded that initial hydrocephalus has no impact on outcome in patients with sellar masses. Overall survival and functional capacity are impaired

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Table 20

Prevalence of Non-functioning Adenomas.				
POPULATION	METHOD	DATABASE	PREVALENCE	REFERENCE
UK, n=81,149	Review of clinical data	16 surgical centers in Banbury	22.2 per 100,000	Fernandez et al. 2010[74]
Sweden adult patients diagnosed with PAs (n=592)	Review of clinical data	Swedish Pituitary Registry	1.8 per 100,000	Tjonstrand et al. 2014[99]
Sweden (n=2,795)	Review of clinical data	Nationwide health registries in Sweden	2 per 100,000	Olsson et al. 2015[100]
Iceland (n=471)	Review of clinical data	All pituitary adenomas diagnosed in Iceland 1955-2012	42.3 per 100,000	Agustsson et al. 2015[73]

Abbreviations: UK, United Kingdom; n, number.

Table 21

Life expectancy and mortality, non-functioning adenomas.					
POPULATION	METHOD	SMR			REFERENCE
		MALES	FEMALES	TOTAL	
UK (n=546)	Retrospective cohort study in a tertiary referral center in the UK	N/A	N/A	SMR was 3.6 (95% CI, 2.9-4.5), for those operated before 1990, 4.7 (95% CI, 2.7-7.6) and for those after 1990, 3.5 (95% CI, 2.8-4.4).	Ntali et al. 2015[102]
Denmark (n=160)	Patient follow-up (mortality calculated 12.4 years after operation)	0.83 (CI 0.55-1.26).	1.97 (CI 1.20-3.21)	1.18 (95% confidence limits (CI) 0.87-1.60).	Lindholm et al. 2006[103]
Sweden (n=2,795) patients with non-functioning pituitary tumors	Review of clinical data	1.29 (CI 1.11-1.48)	1.29; (CI 1.11-1.48)	SMR of 1.10 (1.00-1.20).	Olsson et al. 2015[100]

Abbreviations: SMR, standardized mortality ratio; UK, United Kingdom; n, number; N/A data not available.

Table 22

Key trends and health outcomes of non-functioning adenomas.			
POPULATION	TREATMENT	OUTCOME	REFERENCE
Italy (n=84)	Surgery	In the non-surgical group (33 patients), the macroadenomas showed a 15% probability of tumor growth and reduction. Similar tumor size alterations were observed also for the microadenomas. In the surgical group (51 patients), both classes of tumor remnants (>1 and <1 cm) remain mainly stable postoperatively through the time of last imaging.	Karamouziz et al. 2015[104]
Italy (n=68)	Fractionated radiotherapy for non-functioning pituitary tumors	49 patients had a tumor reduction, 16 remained stable, and three progressed.	Minniti et al. 2015[105]

Abbreviation: n, number.

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in survivors presenting with initial hypothalamic involvement. Progression-free survival is not affected by hydrocephalus, hypothalamic involvement, or degree of resection. Accordingly, gross-total resection is not recommended in sellar masses with initial hypothalamic involvement to prevent further hypothalamic damage.[110]

2.2.1.3

Meningiomas

Prevalence

Meningiomas account for about 1% of sellar masses. Although they can mimic pituitary adenomas, they are more vascularized and invasive.[111]

Demographic Differences

Sellar/suprasellar meningiomas represent 4% of all meningiomas, and have a particularly high female predominance. Sex steroids may play a role in the tumorigenesis of meningiomas, and these tumors may express hormone receptors. Progesterone receptor expression in women with meningioma was significantly higher than in men (OR 2.3; p=0.08).[112]

Kwancharoen et al. performed a retrospective study of 1,516 surgically treated meningiomas between January 2000 and May 2012. Cases were matched to the radiology database to identify a strictly defined sellar and/or suprasellar location. They reported a female-to-male ratio of 6:1, and a mean age of 52 years.[111]

Life Expectancy and Mortality

Raco and colleagues analyzed data of 110 patients with tuberculum sellae meningiomas, operated between 1953 and 1993 at the Neurosurgical Institute, Department of Neurosciences, of Rome "La Sapienza" University. Tumor diameter ranged between 3-9 cm, and most patients presented severe visual loss. In addition, removal was total in 91.3% of cases, and sub-total in 8.7%. The mortality rate was reported at 7.2%. during the post-operativ eperiod.[113] Kwancharoen et al. reported no deaths during their study period.[111]

Key Trends and Health Outcomes

Kwancharoen and colleagues reported that the most common symptoms were visual disturbance (58%), headache (16%), and incidental finding (12%), with a

Table 23

Prevalence of craniopharyngiomas and nonadenomatous sellar lesions.

POPULATION	DATABASE	PREVALENCE	REFERENCE
US subjects undergoing at least one pituitary MRI scan from 1999 to 2009 (n=2,598)	Medical records Pituitary Center, Cedars Sinai Medical Center, Los Angeles, California	Nonadenomatous sellar masses accounted for 18% of visible lesions, of which the most common were Rathke's cleft cyst (19%), craniopharyngioma (15%), and meningioma (15%). Metastases accounted for 5% of non-pituitary lesions and breast cancer was the most common primary source.	Famini et al. 2011[107]
Canada, patients presenting with a sellar mass (n=1,005)	Data from all pituitary-related referrals within the province of Nova Scotia were prospectively collected in interlinked computerized registries starting in November 2005.	There was a population prevalence rate of sellar masses of 0.1%. Of these patients, 837 (83%) had pituitary adenomas and 168 (17%) had non-pituitary lesions. The relative prevalence and standardized incidence ratio, respectively, of various sellar masses were: nonfunctioning adenomas (38.4%; 2.34), prolactinomas (34.3%; 2.22), Rathke's cyst (6.5%; 0.5), GH-secreting adenomas (6.5%; 0.3), craniopharyngiomas (4.5%; 0.2), adrenocorticotropic hormone-secreting adenomas (3.8%; 0.2), meningiomas (1.9%), and others (3.9%; 0.21).	Al-Dahmani et al. 2015[108]

Abbreviations: US, United States; MRI, magnetic resonance imaging.

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mean duration of symptoms of 13 months.[111] In addition, the study reported hyperprolactinemia in 36% of cases, "likely meningioma" in 65%, "possible meningioma" in 8.7%, and pituitary adenoma in 11%. A "dural tail" sign was reported in a third of cases.[111]

After surgery, visual disturbances improved in most patients (80%), but headaches improved only in 7% of patients. Post-operative complications occurred in 38.6% of patients at the 1 month mark, and in 33.3% of cases 3 months after surgery.[111]

2.2.1.4

Metastatic Sellar Lesions

Prevalence and Incidence

Metastatic disease to the sella is uncommon, and there are limited available data regarding the clinical aspects of this disease.[114] Ariel et al. reported that the most common neoplastic sources to the sella were breast and renal cell carcinomas. Specifically, six patients (46%) had breast carcinoma, three (23%) had renal cell carcinoma, two (15%) had squamous cell carcinoma of the head and neck, one had bronchoalveolar carcinoma of the lung, and one had nodular sclerosing Hodgkin's lymphoma.[114]

Secondary hypothyroidism was the most common endocrine abnormality, followed by diabetes insipidus and adrenal insufficiency.[114]

Demographic Differences

In the study by Areil and colleagues nine out of 13 subjects were female. The mean age at diagnosis was 55 years (range, 25 to 73 years).[114]

Key Trends and Health Outcomes

In the study by Ariel, the most common presenting signs and symptoms were headache (58%), followed by fatigue (50%), polyuria (50%), visual field defects (42%), and ophthalmoplegia (42%). Seventy-five percent of patients presented with at least one pituitary hormone insufficiency, which included six patients (50%) with diabetes insipidus. Eight (67%) subjects had secondary hypothyroidism and five (45%) had secondary adrenal insufficiency. Of the patients with stalk involvement, 86% had diabetes insipidus. All patients had a prior diagnosis of malignancy, with a mean duration of 95 months.

2.2.2

INFILTRATIVE LESIONS

Infiltrative lesions include neoplastic lesions discussed above; inflammatory lesions, which include sarcoidosis, xanthoma, lymphocytic and granulomatous hypophystis, and Wegner's granulomatosis; vascular lesions, including aneurysms and apoplexy; and infectious lesions, such as tuberculosis or other infections or abscesses.[115-117]

2.2.2.1

Pituitary Apoplexy

A potentially life-threatening condition associated with sellar lesions is pituitary apoplexy. This rare endocrine emergency usually results from hypothalamic pituitary adrenal axis dysfunction and associated deficiencies in anterior pituitary hormone secretion. Patients usually present with headache, vomiting, altered sensorium, visual defect.

Prevalence and Incidence

The exact incidence of pituitary apoplexy is difficult to estimate, as many cases remain undiagnosed. However, it could occur in up to 21% of non-functioning pituitary tumors. Pituitary apoplexy is often the first presentation of the underlying pituitary tumor in over 80% of patients. Most cases of pituitary apoplexy present in the 5th or 6th decade with a slight male preponderance ranging from 1.1 to 2.25:1.0.[118]

Demographic Differences

In a recent retrospective analysis of 42 pituitary apoplexy patients from 1980 to 2007, the sex ratio was 3:1 with median age of the patients of 53.5 (range 21–85) years.[119] In the largest series from India studied at Vellore, the sex ratio was approximately 2:1 with mean age of presentation of 40.4 (range 18-65) years.[120] A study by Liu et al. showed a slight female preponderance for combined clinical and subclinical cases, however amongst clinical cases it was more common in males.[118,121]

2.2.2.2

Lymphocytic Hypophysitis

Lymphocytic hypophysitis is an uncommon autoimmune disease in which the pituitary gland is infiltrated by lymphocytes, plasma cells, and macrophages that could cause posterior pituitary dysfunction (diabetes insipidus) and/or anterior pituitary dysfunction. Clinicians should suspect lymphocytic hypophysitis in pregnant women and in women with recent delivery presenting with hyperprolactinemia, headache, visual field alterations, and deficiency of one or more pituitary hormones with secondary impairment of related peripheral target glands, especially when associated with other autoimmune

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endocrine or non-endocrine disorders. Lymphocytic hypophysitis can be due to lymphocytic, granulomatous or IgG4-related infiltration of the pituitary and infidibulum—the lymphocytic type is the most common of these.[122] It can also occur less frequently in prepubertal or post-menopausal women and in men.[123]

Prevalence and Incidence

There has been a recent increase in the number of reported cases of lymphocytic hypophysitis (from 1962–1981,16 cases; from 1982–2001, 290 cases, and from 2002-2004, 73 cases).[124] The recent increase in the use of noninvasive pituitary imaging and transsphenoidal surgery likely contributes to the increased diagnosis of lymphocytic hypophysitis, as does the growing general awareness of the condition in the medical community. A 2001 study by Buxton and Robertson reported a 1 per 9 million per year incidence estimate.[124] This may well be an underestimate of today's incidence, especially since some lymphocytic hypophysitis cases may still go undiagnosed because of their indolent, subclinical course.[125]

Demographic Differences

There have been reported cases of lymphocytic hypophysitis in 27 of the 193 sovereign nations of the world, but principally in Japan (34%), the US (22%), the United Kingdom (7%), Germany (7%), and Canada (5%). This might reflect a geographic or ethnic variation in risk, but it is more likely due to variations in diagnosis and/or reporting.[125]

One study reported that lymphocytic hypophysitis is more common in women, with a female-to-male ratio of 6:1, and that woman tend to present at a younger age (35 ± 13 years) than males (45 ± 14 years). In a significant percentage of women lymphocytic hypophysitis manifests during pregnancy or postpartum.[125]

Key Trends and Outcomes

A retrospective analysis conducted from 1997 to 2014 at a single academic center identified 21 patients (13 women and eight men) with lymphocytic hypophysitis with a median diagnosis age of 37.4 years. Patients presented with various symptoms of expanding sellar mass with most common signs including headache (57%), polyuria/polydipsia (52%), vision changes (52%), and amenorrhea or decreased libido (48%). Pre-treatment endocrine evaluation revealed that 12 (57%) patients had complete anterior hypopituitarism, 11 patients (52%) had diabetes insipidus, 10 patients (48%) had mild hyperprolactinemia and three patients (14%) had isolated endocrine axis deficiencies with partial gland function.[122]

Therapy is directed at treating associated anterior and posterior hormone deficiencies and/or hyperprolactinemia and controlling symptoms of headache and visual disturbance that result from mass effect. A patient might need a neurosurgical biopsy to confirm the diagnosis and exclude other neoplastic and infiltrative stalk lesions, which would require different treatments.[123] Despite lack of evidence-based studies, clinicians often prescribe steroids for patients with symptomatic/problematic cases.[126]

Spontaneous remission can occur; so, a careful follow-up is required in all patients including pituitary function testing and sellar imaging. Symptomatic patients will need medical treatments (immunosuppressive, replacement and antiprolactinemic) and neurosurgical treatments (decompression).[123]

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