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Investigation of pituitary disease

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Search strategy

The information in this chapter is taken from standard UK endocrinology clinical practice. It reflects expert opinion (level 4 evidence) with regards to endocrinology tests currently performed in the UK.

Search Strategy

The data in this chapter are supported by a Medline search using the key words prolactin, IGF-1, ACTH stimulation test, dexamethasone suppression test, pituitary function testing, SIADH, diabetes insipidus, Cushing's disease, acromegaly, pituitary adenoma, hypopituitarism,

Key points

Pituitary adenomas can cause local mass effects as well as hyper/hyposecretion of pituitary hormones.

Magnetic resonance imaging of the pituitary is the modality of choice for imaging pituitary pathology.

Visual field assessment using perimetry techniques should be performed on all patients with sella mass lesions that abut the optic chiasm.

The initial hormonal evaluation of a pituitary adenoma will be guided by the history and clinical examination for evidence of hormone insufficiency or excess.

Biochemical diagnosis of pituitary insufficiency is made by demonstrating low levels of trophic hormones in the setting of low target hormone levels. Provocative tests may be required to assess pituitary reserve.

Dynamic pituitary function testing is required for testing the integrity of the ACTH/cortisol axis and determination of GH deficiency or excess.

Water deprivation testing can be useful for the diagnosis of diabetes insipidus.

The pituitary gland lies in the sella turcica which is situated in the middle cranial fossa at the base of the brain. It is linked functionally to the hypothalamus by the pituitary stalk. The anterior pituitary secretes growth hormone (GH), thyrotropin or thyroid-stimulating hormone (TSH), corticotropin or adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH), all of which are under positive stimulatory control, and prolactin (PRL) that is under the inhibitory control of dopamine. The posterior lobe releases arginine vasopressin (also called antidiuretic hormone) and oxytocin.

Investigating anterior pituitary dysfunction

The anterior pituitary hormonal secretion is regulated by hypothalamic releasing and inhibitory factors delivered via portal capillaries, and by negative feedback inhibition of the respective hormones secreted by the target endocrine glands such as the thyroid gland and adrenal cortex.

The presentation of anterior pituitary disease, most commonly associated with a structural lesion, may result from:

(1) local mass effects; causing headache, visual field defects and ocular nerve palsies (2) pituitary hormone deficiencies; producing wide ranging effects as a result of single or multiple deficiencies, with GH and gonadotropins (LH and FSH) usually affected first, followed much later by ACTH and TSH.

(3) pituitary hormone hypersecretion, usually arising as a consequence of neoplastic proliferation of particular cell types within the gland (1, 2).

Investigation includes:

(1) test for hormone hyper- or hyposecretion by measuring TSH and thyroxine, FSH/LH and testosterone or oestradiol and prolactin. Dynamic testing is required for the ACTH/cortisol axis and determination of GH deficiency or excess.

(2) Imaging; MRI is the modality of choice for radiological assessment.

(3) Neuro-ophthalmological evaluation, including assessment of visual acuity and visual fields (3).

Investigating pituitary hormonal hypersecretion.

Pituitary masses may present with a typical clinical syndrome resulting from hypersecretion of one or more anterior pituitary hormones. Alternatively, they may present through compression of surrounding structures such as the optic chiasm or the adjacent normal pituitary, causing

hypopituitarism. Functional pituitary tumours can produce a complex picture of combined hormonal excess and/or deficiencies.

Laboratory Investigation

The presenting clinical features of functional pituitary adenomas (e.g., acromegaly, Cushing's syndrome) guide the laboratory studies. However, for a sellar mass with no obvious clinical features of hormone excess, laboratory studies are geared toward determining the nature of the tumour and assessing the possible presence of hypopituitarism. When a pituitary adenoma is found incidentally on MRI scan, the initial hormonal evaluation will be guided by the history and clinical examination to look for signs of hormone excess including (1) prolactin; (2) insulin like growth factor- 1 (IGF-1); (3) 24-h urinary free cortisol and/or overnight oral dexamethasone (1 mg) suppression test; (4) α-subunit, FSH, and LH; and (5) thyroid function tests (freeT4 and TSH). Additional hormonal evaluation may be indicated based on the results of these tests (Table 1). Pending more detailed assessment of hypopituitarism, 8 A.M. cortisol and testosterone levels, and thyroid function tests usually identify patients with pituitary hormone deficiencies that require hormone replacement before further testing or surgery.

Table 1

Baseline tests to evaluate pituitary hormone hypersecretion

	Tests	Comments
Acromegaly	Serum IGF-I	Interpret IGF-I relative to age- and gender-matched controls
	Oral glucose tolerance test with GH obtained at 0, 60, and 120 min	Normal subjects should suppress growth hormone to <1µg/L
Prolactinoma	Serum prolactin	Prolactin levels can be higher in patients who take medications including antidepressants, antipsychotics and antiemetics as well as some over the counter medications and homeopathic remedies; MRI of the pituitary if prolactin significantly elevated (<2000mU/L)
Cushing's disease	24-h urinary free cortisol	Ensure urine collection is total and accurate ideally with 2 x24 hour samples with measurement of creatinine that should not differ by more than 10%
	Dexamethasone (1 mg) at 11 P.M. and plasma cortisol measured at 8 A.M.	Normal subjects suppress to <1.8µg/dL (< 50nmol/L)
	ACTH assay	Distinguishes adrenal adenoma (ACTH suppressed) from ectopic ACTH or Cushing's disease (ACTH normal or elevated) after biochemical confirmation of hypercortisolemia

Diagnosis of hyperprolactinaemia

Basal morning PRL levels should be measured to assess hypersecretion. It may be necessary to measure prolactin levels on different occasions when clinical suspicion is high. Since prolactin may be elevated as a stress response in a random sample, cannulated prolactin levels with samples taken through a cannula at 60 minute intervals after insertion to reduce this stress response can be helpful(5). In patients with markedly elevated PRL levels (>2000mU/L), results may be falsely lowered because of assay artefacts (the high dose hook effect); sample dilution is required to measure these high values accurately, however, it is rare with modern assays. Falsely elevated values may be caused by aggregated forms of circulating PRL, which are biologically inactive (macroprolactinemia)(6). Hypothyroidism should be excluded by measuring serum TSH and T4 levels.

Diagnosis of acromegaly

Age- and gender-matched serum IGF-I levels are elevated in acromegaly. Consequently, an IGF-I level provides a useful laboratory screening measure when clinical features raise the possibility of acromegaly. Due to the pulsatility of GH secretion, measurement of a single random GH level is not useful for the diagnosis or exclusion of acromegaly and does not correlate with disease severity. The diagnosis of acromegaly is confirmed by demonstrating the failure of GH suppression to <1 μg/L within 1–2 h after a 75 g oral glucose load(7). PRL is elevated in approximately a quarter of patients with acromegaly. Thyroid function, gonadotropins, and sex steroids may be reduced because of tumour mass effects. Since most patients will undergo surgery with glucocorticoid coverage, tests for ACTH reserve in asymptomatic patients could be deferred until after surgery.

Diagnosis of Cushing's disease

The diagnosis of Cushing's syndrome is based on laboratory documentation of endogenous hypercortisolism(9). Measurement of 24-h urine free cortisol is often used as the screening test, ideally two collections with measurement of creatinine that should not differ by more than 10% to indicate adequacy of collection. Alternatively, the failure to suppress plasma cortisol after an overnight 1mg dexamethasone suppression test can be used to identify patients with hypercortisolism. However, this test has a false positive rate of 2% in the normal population, 13% in obese subjects and 23% in hospital inpatients and is not favoured by many clinicians. A low dose dexamethasone suppression test is also used to confirm hypercortisolemia, which has a higher sensitivity of 98% for screening Cushing's syndrome. This is done by administering 0.5mg of dexamethasone 6 hourly for 48 h at 9 a.m., 3p.m., 9 p.m. and 3 a.m., and should lead to complete suppression of cortisol to <50 nmol/L in normal subjects with serum cortisol measurement at baseline and 48hours. As nadir levels of cortisol occur at night, elevated midnight samples of cortisol are suggestive of Cushing's syndrome and this test will require admission to hospital. More recently, however, midnight salivary free measurements have been used which are simpler. Basal plasma ACTH levels often distinguish patients with ACTH-independent (adrenal or exogenous glucocorticoid) from those with ACTH-dependent (pituitary, ectopic ACTH) Cushing's syndrome (10). Mean basal ACTH levels are about eightfold higher in patients with ectopic ACTH secretion compared to those with pituitary ACTH-secreting adenomas. However, extensive overlap of ACTH levels between these two disorders (ectopic ACTH versus pituitary ACTH-secreting adenoma) precludes using ACTH to make the distinction (11).

If the investigations are highly suggestive of pituitary Cushing's disease then pituitary MRI with gadolinium enhancement is undertaken but is often not sensitive enough to detect small (<2 mm) pituitary ACTH-secreting adenomas. In this case, bilateral inferior petrosal sinus ACTH sampling before and after corticotropin-releasing hormone (CRH) administration may

be required to distinguish a pituitary lesion from ectopic ACTH-secreting tumours that may have similar clinical and biochemical characteristics(12). Simultaneous assessment of ACTH concentrations in each inferior petrosal vein and in the peripheral circulation provides a strategy for confirming and localizing pituitary ACTH production. Sampling is performed at baseline and 2, 5, and 10 min after intravenous bovine CRH (1 μg/kg) injection. An increased ratio (>2) of inferior petrosal to peripheral vein ACTH confirms pituitary Cushing's syndrome. After CRH injection, peak petrosal-to-peripheral ACTH ratios of ≥3 confirm the presence of a pituitary ACTH-secreting tumour when there is unequivocal endogenous hypercortisolaemia. The sensitivity of this test is >95%, with rare false-negative results encountered in patients with aberrant venous drainage. Petrosal sinus catheterizations are technically difficult, and about 0.05% of patients develop neurovascular complications.

Most ACTH-secreting pituitary tumours are <5 mm in diameter, and about half are undetectable by sensitive MRI. The high prevalence of incidental pituitary microadenomas diminishes the ability to distinguish ACTH-secreting pituitary tumours accurately by MRI.

TSH secreting adenomas

TSH-producing macroadenomas are rare but are often large and locally invasive when they occur. Patients usually present with thyroid goitre and hyperthyroidism, reflecting overproduction of TSH. Diagnosis is based on demonstrating elevated serum free T4 levels, inappropriately normal or high TSH secretion, and MRI evidence of a pituitary adenoma(13). The commonest cause of elevated FT4 and normal or high TSH is failure to comply with treatment for hypothyroidism and taking thyroxine supplementation a few days prior to thyroid function tests. It is, however, also important to exclude other causes of inappropriate TSH secretion, such as resistance to thyroid hormone, an autosomal dominant disorder caused by

mutations in the thyroid hormone β receptor and resistance to thyrotopin (14). The presence of a pituitary mass and elevated α-subunit levels are suggestive of a TSH-secreting tumour.

Diagnosis of non-functioning and gonadotropin secreting pituitary adenoma

Clinically non-functioning tumours often present with optic chiasm pressure and other symptoms of local expansion or may be incidentally discovered on an MRI performed for another indication(16). Menstrual disturbances or ovarian hyperstimulation rarely occur in women with large tumours that produce FSH and LH. More commonly, adenoma compression of the pituitary stalk or surrounding pituitary tissue leads to attenuated LH and features of hypogonadism. PRL levels are usually slightly increased due to stalk compression. Most non-functioning tumours respond poorly to medical treatment, but can be given an empirical treatment with a dopamine agonist, unless decompression of the chiasm is warranted if prolactin levels are raised.

Free α-subunit levels may be elevated in 10–15% of patients with non-functioning tumours. In female patients, peri- or postmenopausal basal FSH concentrations are difficult to distinguish from tumour-derived FSH elevation.

Testosterone levels are usually low, despite the normal or increased LH level, perhaps reflecting reduced LH bioactivity or the loss of normal LH pulsatility. Because this pattern of hormone levels is also seen in primary gonadal failure and with ageing, the finding of increased gonadotropins alone is insufficient for the diagnosis of a gonadotropin-secreting tumour. For non-functioning and gonadotropin-secreting tumours, the diagnosis usually rests on immunohistochemical analyses of resected tumour tissue, as the mass effects of these tumours usually necessitate resection (16). Although acromegaly or Cushing's syndrome usually

present with unique clinical features, clinically unapparent somatotroph or corticotroph adenomas can be excluded by a normal IGF-I value and normal 24-h urinary free cortisol levels.

Radiological Imaging

Magnetic resonance imaging (MRI)

Sagittal and coronal T1-weighted MRI imaging, before and after administration of gadolinium, allows precise visualization of the pituitary gland with clear delineation of the surrounding structures. Adenoma density is usually lower than that of surrounding normal tissue on T1-weighted imaging, and the signal intensity increases with T2-weighted images. The high phospholipid content of the posterior pituitary results in a "pituitary bright spot."

Sellar masses are commonly encountered as incidental findings on MRI, and most of these are incidentalomas. In the absence of hormone hypersecretion, these small lesions can be safely monitored by MRI, which is performed annually and then less often if there is no evidence of growth. Resection may be considered for incidentally discovered macroadenomas, as about one-third become invasive or cause local pressure effects. If hormone hypersecretion is evident, specific therapies are indicated. When larger masses (>1 cm) are encountered, they should also be distinguished from non-adenomatous lesions including meningiomas (associated with bony hyperostosis), craniopharyngiomas (usually calcified and hypodense) and gliomas (hyperdense on T2-weighted images).

Ophthalmologic Evaluation

Visual field assessment that uses perimetry techniques should be performed on all patients with sellar mass lesions that abut the optic chiasm. Bitemporal hemianopia or superior bitemporal defects are classically observed, reflecting the location of these tracts within the inferior and

posterior part of the chiasm. Homonymous cuts reflect postchiasmal lesions and monocular field cuts prechiasmal lesions.

Histologic Evaluation

Immunohistochemical staining of pituitary tumour specimens obtained at transsphenoidal surgery confirms clinical and laboratory studies and provides a histologic diagnosis when hormone studies are equivocal and in cases of clinically non-functioning tumours.

Investigating anterior pituitary hormonal hyposecretion (hypopituitarism)

The clinical manifestations of hypopituitarism depend on which hormones are lost and the extent of the hormone deficiency. Biochemical diagnosis of pituitary insufficiency is made by demonstrating low levels of trophic hormones in the setting of low target hormone levels(1). For example, low free thyroxine in the setting of a low or inappropriately normal TSH level suggests secondary hypothyroidism. Similarly, a low testosterone level without elevation of gonadotropins suggests hypogonadotropic hypogonadism.

Provocative tests may be required to assess pituitary reserve (17). GH responses to insulin-induced hypoglycemia, arginine, l-dopa, growth hormone–releasing hormone (GHRH), or growth hormone–releasing peptides (GHRPs) can be used to assess GH reserve. Corticotropin-releasing hormone (CRH) administration induces ACTH release, and administration of synthetic ACTH [cosyntropin (Cortrosyn)] evokes adrenal cortisol release as an indirect indicator of pituitary ACTH reserve.

ACTH reserve is most reliably assessed during insulin induced hypoglycemia(18). However, this test should be performed cautiously in patients with suspected adrenal insufficiency because of enhanced susceptibility to hypoglycaemia and hypotension. Insulin-induced hypoglycaemia is contraindicated in patients with active coronary artery disease or seizure

disorders. The glucagon stimulation test is also used for dynamic pituitary function testing and can be used safely when insulin is contraindicated.

Table 2

TESTS OF PITUITARY SUFFICIENCY

Dynamic pituitary hormonal testing

Hormone	Test	Blood samples	Interpretation
Growth hormone (19)	Insulin tolerance test: Regular insulin (0.05–0.15 U/kg IV)	–30, 0, 30, 60, 120 min for glucose and GH	Glucose <40 mg/dL (2mmol/L); GH should be >3 µg/L(5mU/l)
	Glucagon stimulation test: 0.5 – 1.5mg of glucagon IM	0, 30, 60, 90, 120, 150, 180, 210, 240 min for GH	Peak GH should be >3 µg/L (5mU/l)
	GHRH test: 1µg/kg IV	0, 15, 30, 45, 60, 120 min for GH	Normal response is GH>3 µg/L (5mU/l)
	L-Arginine test: 30 g IV over 30 min	0, 30, 60, 120 min for GH	Normal response is GH>3 µg/L (5mU/l)
	L-dopa test: 500 mg PO	0, 30, 60, 120 min for GH	Normal response is GH>3 µg/L (5mU/l)
ACTH	Insulin tolerance test(18): Regular insulin (0.05–0.15 U/kg IV)	–30, 0, 30, 60, 120 min for glucose and GH	Glucose <40 mg/dL (2mmol/L); Cortisol should increase by >7µg/dL (180nmol/L) or to >20µg/dL (550nmol/L)
	Glucagon stimulation test: 0.5 – 1.5mg of glucagon IM	0, 30, 60, 90, 120, 150, 180 ,210, 240 min for cortisol	Cortisol should increase by >7µg/dL (180nmol/L) or to >20µg/dL (550nmol/L)
	CRH test: 1µg/kg CRH IV at 0800 h	0, 15, 30, 60, 90, 120 min for ACTH and cortisol	Basal ACTH increases two- to fourfold and peaks at 20–100 pg/mL Plasma cortisol should be <4µg/dL to ensure an adequate response.
	Metyrapone test(20): Metyrapone (30 mg/kg) at midnight	Plasma 11-deoxycortisol and cortisol at 8 A.M.; ACTH can also be measured	Normal response is 11-deoxycortisol >7.5µg/dL or or ACTH >75 pg/mL

	Standard ACTH stimulation test: ACTH 1-24 (Cosyntropin), 0.25 mg IM or IV Low-dose ACTH test: ACTH 1-24 (Cosyntropin), 1µg IV 3-day ACTH stimulation test consists of 0.25 mg ACTH 1-24 given IV over 8 h each day	0, 30, 60 min for cortisol and aldosterone 0, 30, 60 min for cortisol 0 and 72 hr for cortisol	Normal response is cortisol >21µg/dL and aldosterone response of >4 ng/dL above baseline. Cortisol should be >21µg/dL Cortisol should be >21µg/dL
TSH	Basal thyroid function tests: T4, T3, TSH TRH test: 200–500µg IV: 0, 20, 60 min for TSH and PRL	Basal tests	Low free thyroid hormone levels in the setting of TSH levels that are not appropriately increased TSH should increase by >5 mU/L unless thyroid hormone levels are increased. Evoked prolactin response indicates lactotrope integrity
LH, FSH	Basal LH, FSH, testosterone, oestrogen GnRH test: GnRH (100 µg) IV	 0, 30, 60 min for LH and FSH	Basal LH and FSH should be increased in postmenopausal women Low testosterone levels in the setting of low LH and FSH In most adults, LH should increase by 10 IU/L and FSH by 2 IU/L Normal responses are variable
Multiple hormones	Combined anterior pituitary test: GHRH	–30, 0, 15, 30, 60, 90, 120 min for GH,	Combined or individual release hormone

	(1µg/kg), CRH (1µg/kg), (or insulin stress test or glucagon stimulation test), GnRH (100µg), TRH (200 µg) are given IV	ACTH, cortisol, LH, FSH and TSH	responses must be elevated in the context of basal target gland hormone values and may not be uniformly diagnostic

Investigating posterior pituitary dysfunction

The neurohypophysis, or posterior pituitary gland, is formed by axons that originate in large cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus. It produces two hormones: (1) arginine vasopressin (AVP), also known as antidiuretic hormone; and (2) oxytocin. AVP acts on the renal tubules to reduce water loss by concentrating the urine. Oxytocin stimulates postpartum milk letdown in response to suckling. AVP deficiency causes diabetes insipidus (DI), characterized by the production of large amounts of dilute urine. Excessive or inappropriate AVP production predisposes to hyponatremia if water intake is not reduced in parallel with urine output.

Deficiency of AVP secretion

Diabetes insipidus

Decreased secretion or action of AVP characterized by the production of abnormally large volumes of dilute urine. The 24-h urine volume is >50 mL/kg body weight and the osmolarity is <300 mOsmol/L. The polyuria produces symptoms of urinary frequency, enuresis, and/or nocturia, which may disturb sleep and cause mild daytime fatigue or somnolence. It is also associated with thirst and a commensurate increase in fluid intake (polydipsia). Clinical signs of dehydration are uncommon unless fluid intake is impaired.

Investigation

When clinically suspected, a 24-h urine should be collected on an ad libitum fluid intake to confirm polyuria. If the volume exceeds 50 mL/kg per day, polyuria is present. If the osmolarity is >300 mOsmol/L, the polyuria is due to a solute diuresis and the patient should be evaluated for glucosuria or other less common causes of excessive solute excretion. However, if the 24-h urine osmolarity is <300 mOsmol/L, the patient has a water diuresis and should be evaluated further to determine which type of DI is present.

Except in the rare patient who is clearly dehydrated under basal conditions of ad libitum fluid intake, the evaluation should begin with a fluid deprivation test. The test should be started in the morning and water balance should be monitored closely with hourly measurements of body weight, plasma osmolarity and/or sodium concentration, and urine volume and osmolarity.

If fluid deprivation does not result in urine concentration (osmolarity >300 mOsmol/L, specific gravity >1.010) before body weight decreases by 5% or plasma osmolarity/sodium exceed the upper limit of normal, the patient has severe pituitary or severe nephrogenic DI. These disorders can usually be distinguished by administering desmopressin (DDAVP, 0.03 μg/kg SC or IV) and repeating the measurement of urine osmolarity 1–2 h later. An increase of >50% indicates severe pituitary DI, whereas a smaller or absent response is strongly suggestive of nephrogenic DI.

The differential diagnosis of DI may also be facilitated by MRI of the pituitary and hypothalamus. In most healthy adults and children, the posterior pituitary emits a hyperintense signal in T1-weighted mid-sagittal images. This “bright spot” is almost always present in patients with primary polydipsia but is invariably absent or abnormally small in patients with pituitary DI. It is usually also small or absent in nephrogenic DI, presumably because of high secretion and turnover of vasopressin. A normal bright spot virtually excludes pituitary DI, is unlikely in nephrogenic DI, and strongly suggests primary polydipsia.

Excess vasopressin secretion

Syndrome of inappropriate ADH secretion (SIADH)

Excessive secretion or action of AVP results in the production of decreased volumes of more highly concentrated urine. If not accompanied by a commensurate reduction in fluid intake or an increase in insensible loss, the reduction in urine output results in excess water retention with expansion and dilution of all body fluids. In some patients, excessive intake results from inappropriate thirst. If the hyponatremia develops gradually or has been present for more than a few days, it may be largely asymptomatic. However, if it develops acutely, it is almost always accompanied by symptoms and signs of water intoxication that may include mild headache, confusion, anorexia, nausea, vomiting, coma, convulsions and could be lethal.

Aetiology

Hyponatremia and impaired urinary dilution can be caused by a primary defect in the regulation of AVP secretion or action or can be secondary to a recognized non-osmotic stimulus such as hypovolemia, hypotension, nausea, or glucocorticoid deficiency. The primary forms are generally referred to as syndromes of inappropriate ADH secretion (SIADH). They have many different causes, including ectopic production of AVP by lung cancer or other neoplasms; eutopic release by various diseases or drugs; and exogenous administration of AVP, desmopressin, or large doses of oxytocin.

SIADH is a diagnosis of exclusion that can usually be accomplished with routine historic, physical, and laboratory information. In a patient with hyponatremia, the possibility of simple dilution caused by an osmotically driven shift of water from the intracellular to the extracellular space should be excluded by measuring plasma glucose and/or plasma osmolarity. Normal results of liver function tests, lipids, and glucose concentration exclude rare causes of artifactual pseudohyponatraemia (hyperproteinaemia and hyperlipidaemia) or hyperosmolar

hyponatraemia, where water moves from the intracellular to the extracellular compartment (in severe hyperglycaemia).

SIADH needs to be confirmed by results of paired serum and urine samples: serum hyposmolality must be <275 mOsm/kg (normal range: 275-295 mOsm/kg), and urine osmolality >100 mOsm/kg and sodium ≥30 mmol/L, in the absence of hypovolaemia, hypervolaemia, adrenal or thyroid dysfunction and use of diuretics (21, 22). Paired serum and spot urine samples need to be sent for osmolality and sodium to confirm both hyponatraemia and SIADH. Serum osmolality measurement is not necessary when there is an obvious contributory cause. It can confirm true hyponatraemia (<275 mOsmol/kg) and rules out the rarer hyperosmolar hyponatraemia and pseudohyponatraemia (serum osmolality ≥275 mmol/L).(23)

Urine osmolality (normal range 300-900 mOsm/kg) is needed to confirm SIADH but it also helps in differentiating it from two other conditions. By definition, SIADH is an incomplete suppression of antidiuretic hormone (urine osmolality >100 mOsm/kg); a spot urinary osmolality <100 mOsm/kg indicates appropriate complete suppression. Complete suppression of antidiuretic hormone is seen in psychogenic polydipsia (history of mental illness) and malnutrition (history of heavy alcohol consumption)(24).

Urinary sodium concentration is helpful when the cause of hyponatraemia is not apparent from the history and examination or when SIADH is suspected. In euvolaemic hyponatraemia (including SIADH), the urinary sodium is ≥30 mmol/L (22, 25). Hypervolaemic hyponatraemia should be apparent clinically; because of the reduced effective circulating volume, the kidney concentrates the urine (>100 mOsm/kg) and conserves sodium (<30 mmol/L; but it can be higher when the patient is taking diuretics)(22). The clues to hypovolaemia in the history include obvious fluid loss (through diuretics, for example) or third space fluid loss, when fluid

with high sodium content is sequestered in a body space, as occurs in burns patients. The urinary sodium concentration in all hypovolaemic hyponatraemia is <30 mmol/L except when the kidney is the site of the loss, for example with diuretic use, salt losing nephropathy, or mineralocorticoid deficiency.(26)

When the fluid status is difficult to determine clinically, low serum concentrations of urea and uric acid indicate SIADH, and a raised concentration of urea is more likely to reflect hypovolaemia(24).

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