***ADH Disorders***

[(Central) Diabetes Insipidus 1](#_Toc206262448)

[Nephrogenic Diabetes Insipidus 3](#_Toc206262449)

[Syndrome of inappropriate ADH secretion (SIADH) 4](#_Toc206262450)

**Central** **(s.** **vasopressin-sensitive) diabetes insipidus** – ADH deficiency.

**Nephrogenic diabetes insipidus** (NDI) – renal ADH resistance.

**triple-phase response** – sequence of problems of water balance observed after *head injury* or *pituitary surgery*:

Early – diabetes insipidus

At 4- 7 days – inappropriate antidiuresis

Later – return either to normal or to diabetes insipidus

(Central) Diabetes Insipidus

Etiology

Deficiency of vasopressin (ADH) – due to marked decrease in ***supraoptic & paraventricular nuclei***.

* 10% of neurosecretory neurons must remain to avoid central DI.
* *simple* neurohypophysis *destruction* leads to temporary, unsustained DI (ADH is synthesized within hypothalamus).

**Primary DI**.

* *idiopathic* (30% of all DI cases)
* aprašyta autosomal dominant *vasopressin gene abnormalities* (chromosome 20).

**Secondary (acquired) DI:**

1. supra- and intra-sellar neoplasms (30% of all DI cases)
2. cranial injuries (esp. basal skull fractures) (30% of all DI cases)
3. hypophysectomy
4. Langerhans' cell-type histiocytosis (Hand-Schüller-Christian disease), granulomas (sarcoidosis, tuberculosis)
5. vascular lesions (aneurysm, thrombosis)
6. infections (encephalitis, meningitis,lymphocytic hypophysitis).

Symptoms & Signs

**Polyuria** of very dilute (but otherwise normal) urine → excessive **thirst** **& polydipsia**.

* may occur at any age; onset insidious or abrupt.
* diurezė gali siekti 30 L/day.
* nocturia and thirst awake at night.
* urine is very dilute (sp. gr. < 1.005 and osmolality < 200 mOsm/L).

N.B. jei Uosm > 200 mOsm/L, įtark osmotic diuresis! – tirk šlapime gliukozę, urea, bikarbonatus (jei šlapimo pH > 6).

* dauguma pacientų vedami troškulio palaiko hidrataciją ir natremiją normos ribose (plasma osmolality is high normal);

infants or unconscious patients may rapidly develop life-threatening ***dehydration & hypernatremia***.

N.B. polydipsia keeps patients healthy!

Diagnosis

1. **Water deprivation (dehydration) test** - simplest and most reliable test – sufficient test for diagnosis!

based on principle - in normal persons *increasing plasma osmolality* will lead to *water conservation* (decreased excretion of urine with increased osmolality).

* performed only under **constant supervision**:
	1. for DI patients test may be hazardous
	2. compulsive water drinkers may be unable to avoid drinking unless prevented.
* test is ***started*** in morning:
	+ - 1. patient weight
			2. venous blood – electrolytes & osmolality
			3. urine - osmolality.
* testo metu neleidžiama nei gerti, nei valgyti.
* voided ***urine is collected*** hourly → sp. gr. / osmolality (preferable) is measured.
* ***dehydration is*** ***terminated*** when:
	1. urinary concentration increase is ≤ 0.001 sp. gr. / ≤ 30 mOsm/L in sequentially voided specimens (or three consecutive determinations of urine osmolality are within 10% of each other).
	2. orthostatic hypotension / postural tachycardia appear.
	3. ≥ 5% of initial body weight has been lost.
* again serum electrolytes & osmolality → 5 U aqueous vasopressin sc.
* 60 min postinjection final urine is collected for sp. gr. / osmolality → ***test is terminated***. (paprastai testas trunka ne daugiau 14 valandų).

|  |  |  |  |
| --- | --- | --- | --- |
| **condition** | **maximum Uosm after dehydration** | **plasma [ADH]** | **Uosm after vasopressin SC** |
| *Normal* | > 800(sp. gr. > 1.020) | ↑ | little (≤ 5%) or no effect |
| *Neurogenic DI* | < 300 (i.e. no greater than plasma osmolality) | nondetectable | ↑↑↑ (> 50%) |
| *Nephrogenic DI* | 300-500 | ↑↑↑(> 5 pg/mL) | no effect |
| *Compulsive polydipsia* | > 500(resistance to ADH) | ↑(< 5 pg/mL) | little or no effect |

1. **Hypertonic saline infusion** (normally sharply reduces diuresis) – *not recommended*:
	* dangerous in patients unable to tolerate saline load (e.g. limited cardiac reserve);
	* cannot be interpreted in patients developing salt diuresis.
2. **Plasma [ADH]** - most direct method for diagnosing DI (but *unnecessary*, because water deprivation test is so accurate).
* measured after dehydration or infusion of hypertonic saline.
* not routinely available.
1. **MRI** - absence of normal high signal of neurohypophysis (if MRI negative, repeat within 6 months - morphological abnormalities may appear much later than endocrine symptoms).

Differential Diagnosis

**Various causes of polyuria:**

**1. Osmotic diuresis**

**2. Compulsive polydipsia (s.** **dipsogenic diabetes insipidus)**

* may ingest and excrete up to 6 L of fluid/day (can lead to life-threatening hyponatremia).
* do not have nocturia.
* plasma osmolality is low (vs. in DI) and endogenous ADH is suppressed.
* in water deprivation test, Uosm increases to hypertonic (but submaximal) levels, without further response to exogenous vasopressin.
* chronic water intake diminishes renal medullary tonicity (“washout” of concentration gradient) → *resistance to ADH* (ribojant skysčius, atsistato tik po kelių savaičių!).

Treatment

Negydant, permanent renal damage can result!

**Hormone replacement therapy** see 2488 p.

**Aqueous vasopressin**

* can be given SC, i/m, intranasally, IV drip
* start at 0.5-1 unit/hr and titrate by 1-2 units/hr every 10-60 mins for goal UOP 75-125 mL/hr.
* effect lasts ≤ 6 h.
* side effects (mediated through V1 receptor) - coronary vasospasm, bronchospasm.

**Desmopressin acetate (DDAVP, 1-deamino-8-D-arginine vasopressin)**

* can be given intranasally, SC, i/v.
* *prolonged antidiuretic activity* (lasting 12-24 h) - preparation of choice for both adults and children.
* dozės nustatomos individualiai (plačios variacijos tarp skirtingų pacientų):
* usual dosage in adults is 10-40 µg/day in two divided doses.
* overdosage can lead to fluid retention and convulsions in small children (H: furosemide).
* side effects – headache, slight BP increase.
* when intranasal delivery is inappropriate, it may be administered SC using 1/10 intranasal dose.

**Lypressin (lysine-8-vasopressin)** given by nasal spray at 3-8 h intervals.

**Vasopressin tannate** **in oil** i/m may control symptoms for up to 96 h.

**Nonhormonal therapy** - avoids hypersensitivity and vascular effects of exogenous ADH.

* + 1. **Thiazides** (in traditional doses) paradoxically reduce urine volume (up to 25-50%)
* veikimo mechanizmas: reduce extracellular fluid volume → increased proximal tubular resorption of NaCl & water (collecting ducts pasiekia sumažintas šlapimo kiekis); dėl natriurijos Uosm nenukrenta žemiau 300.
* **salt intake restriction** reduces urine output by reducing solute load.
	+ 1. **ADH-releasing drugs** (chlorpropamide, carbamazepine, clofibrate) effective only in *partial central DI* when residual ADH is present.
* chlorpropamide also potentiates ADH action on kidney.
* may be used with thiazides.
	+ 1. **Prostaglandin inhibitors** (indomethacin) - modestly effective (perhaps by decreasing renal blood flow and glomerular filtration rate).

Nephrogenic Diabetes Insipidus

Renal collecting ducts resistance to ADH (with otherwise normal renal function).

**Inherited** **NDI** - X-linked recessive (***V2 receptoriaus*** defektas).

* *homozygotes* (all males) are completely unresponsive to ADH.
* *heterozygous* females show normal or slightly impaired responsiveness to ADH.
* aprašytas ir ***aquaporin-2*** defektas.

**Acquired NDI** occurs in disorders that disrupt medulla or distal nephrons:

* + 1. medullary and polycystic disease; medullary sponge kidney; pyelonephritis (destruction of medulla).
		2. release of obstructing periureteral fibrosis
		3. sickle cell anemia (RBC sickling in vasa recta)
		4. hypokalemia, hypercalcemia (impaired renal concentrating ability).
		5. amyloidosis; Sjögren's syndrome; myeloma.
		6. nephrotoxins (lithium, demeclocycline).

Symptoms & Signs, Diagnosis

* symptoms (polyuria, polydipsia, and hypotonic urine) appear *soon after birth*.
* infants cannot communicate thirst → **severe water depletion** with hypernatremia, fever, vomiting, and convulsions.

N.B. **brain damage** with permanent mental retardation may occur if treatment is delayed.

* physical growth is often retarded because of frequent dehydration.

Laboratory data:

* Uosm (50-100 mOsm/kg) may rise to 280 mOsm/kg during solute diuresis.
* diuresis is directly related to volume of water delivered to collecting ducts.

Diagnosis - water deprivation test.

Treatment

1. ensure **adequate free water intake** (serious sequelae are rare if patient can increase water intake in response to thirst).
2. modest **Na restriction, thiazide diuretics** (!)**, indomethacin**.

Syndrome of inappropriate ADH secretion (SIADH)

definition - less than maximally dilute urine in presence of plasma hypo-osmolality & hyponatremia.

Etiology

**CNS disorders** (infections, stroke, acute intermittent porphyria, acute psychosis, Guillain-Barré syndr.).

**Drug-induced SIADH** (chlorpropamide, clofibrate, carbamazepine).

***Ectopic ADH secretion* –** various **malignancies** (esp. pulmonary oat cell carcinoma!).

***Stimulation of J receptors in pulmonary circulation*** – various **pulmonary disorders** (pneumonia, lung abscess, tbc, aspergillosis, PEEP).

Abnormal patterns of ADH release:

1. sustained ADH release (apparently independent of osmotic control)
2. abnormally low osmotic threshold for ADH release (“reset osmostat”).
3. constant low-level ADH release - within normal range of plasma osmolality, it is appropriate, but when plasma becomes hypo-osmotic, ADH release is not suppressed.
4. unable to maximally dilute urine (excrete water load), but have normal ADH release - **syndrome of inappropriate antidiuresis** (rather than SIADH); diagnosed only by plasma [ADH] assay.







signs & symptoms, diagnosis

1. **water intoxication**
2. compensatory (due to ECF↑) suppressed aldosterone secretion → **hypernatriuria & hyponatremia** (“salt wasting”).
* Uosm > Posm ; urinary [Na] > 20 mEq/L !!!
* kliniką lemia hiponatremija!!!
* dėl hiponatremijos edemos ir hipertenzija neišreikštos.

Diagnosis relies on:

absence of: volume depletion / overload, emotional stress / pain, diuretics, drugs that stimulate ADH secretion.

presence of: normal cardiac, hepatic, renal, adrenal, and thyroid function.

Treatment

 dar žr. hiponatremijos gydymas (aukščiau)

**Severe water restriction** (25-50% of maintenance – i.e. 500-1000 ml/d).

* eliminates ADH effect (→ normonatremia).
* limiting factor is patient compliance.

Demeclocycline (900-1200 mg/day; efektas po 4-5 d.)

blocks ADH effect on kidney (sukeliamas nephrogenic diabetes insipidus).

indicated when underlying disease is not treatable and severe water restriction is unacceptable.

associated with ***acute renal failure*** in patients with *hepatic cirrhosis*!

Jei hiponatremija labai sunki→ **hypertonic 3% saline** i/v.

Conivaptan (Vaprisol®) – antagonist of vasopressin receptors (V1A and V2) - FDA approved for treatment of **euvolemic hyponatremia** (e.g. SIADH, or in setting of hypothyroidism, adrenal insufficiency, pulmonary disorders).

tolvaptan (Samsca®) – oral vasopressin V2-receptor antagonist

*Panaudota literatūra*:

NMS Surgery, Medicine, Emergency Medicine, Pediatrics, Physiology

Merck Manual 1999