Hypothalamic diseases with endocrine disturbances

Dr. Peter Igaz MD PhD

2nd Department of Medicine
Faculty of Medicine
Semmelweis University

Causes of hypothalamic dysfunction

- Tumors (astrocytoma, glioma, germinoma, craniopharyngeoma, large pituitary tumor, lymphoma)
- Haemorrhages
- Developmental abnormalities (arachnoideal cyst, holoprosencephaly)
- Granulomatous inflammation (histiocytosis X, sarcoidosis, TBC)
- inflammation (encephalitis, meningitis)
- Trauma
- Irradiation
- Hereditary diseases

Diseases of the hypothalamus

- **Deficiency of trophormones (CRH, TRH, GnRH, GHRH) – growth failure, hypopituitarism, disorders of sexual development (isolated GnRH-deficiency – Kallmann-syndrome)**
- **Deficiency of posterior pituitary hormones**
- **Non-endocrine consequences of hypothalamic damage:**
  - **Feeding disorders (anorexia, hyperphagia, obesitas)**
  - **Disorders of fluid intake (adipsia, polydipsia)**
  - **Disorders of thermoregulation (hyperthermia, hypothermia)**
  - **Somnolentia, coma, lightmindedness**
  - **Mood lability**

Kallmann syndrome

- Isolated GnRH deficiency.
- Migration defect of GnRH neurons from olfactory placod to hypothalamus.
- XR, AD or AR
- Secondary hypogonadism (low LH, FSH with low sex steroids) + anosmia/hyposmia
- MRI may show hypoplastic olfactory bulb
- Prevalence: 1:7500, more frequent in men

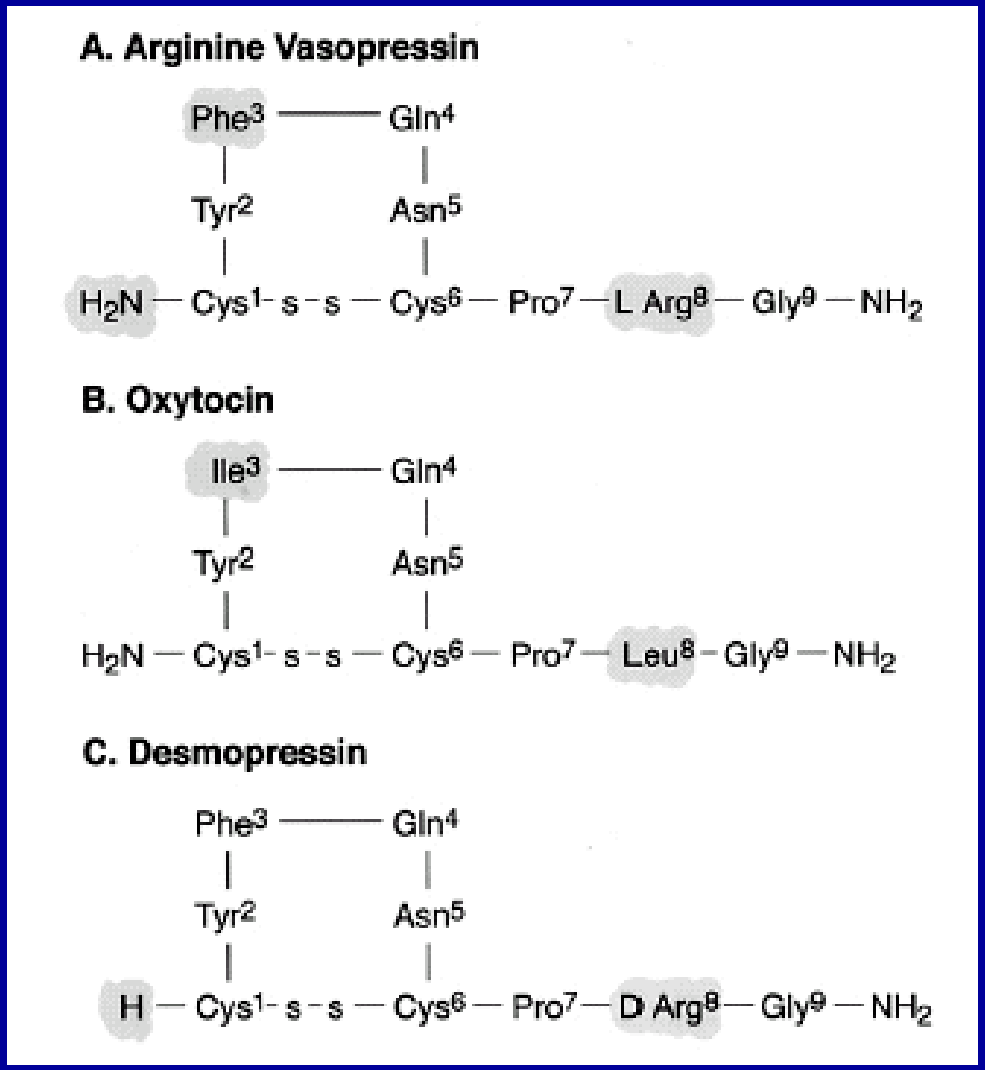
Hypothalamic forms of obesity

- **Dystrophia adiposogenitalis (Fröhlich-syndrome)**
  - obesity, hypogonadism, visual disturbances, skeletal malformations, white skin, intracrnaial tumor
- **Laurence-Moon-Biedl syndrome (AR, 1:160.000)**
  - Laurence-Moon: obesity, spastic paraparesis, retinitis pigmentosa, mental retardation, hypogonadis
  - Biedl-Bardet: polydactily, retinitis pigmentosa, mental retardation, hypogonadism, renal malformations
- **Prader-Willi-Labhart syndrome**

Prader-Willi-Labhart syndrome

GnRH deficiency, obesity, short stature, hypotony of the newborn, Diabetes mellitus type 1, strabismus, scoliosis, mental retardation.

Chemical structure of posterior pituitary hormones



Some basic definitions

- Polydipsia: exaggereted fluid intake
- Polyuria: increased urine
- Adipsia: loss of thirst sensing

DIABETES INSIPIDUS

Major forms of diabetes insipidus

- Central diabetes insipidus.
- Nephrogenic diabetes insipidus.
- Transitional diabetes insipidus in pregnancy (increased metabolism of ADH)
- „Primary polydipsia.” – primarily with psychiatric diseases – major problem in differential diagnosis.

Major causes of centralis diabetes insipidus

- Not a frequent disease, incidence: 4/100.000 person/year.
- Major causes:
  - Trauma
  - Neurosurgery (pituitary tumor)
  - Tumors of hypothalamus and pituitary
  - Rare inflammatory diseases (histiocytosis X, sarcoidosis)
  - Intracranial bleeding, Sheehan syndrome.
  - Very rare congenital forms.

Major symptoms and diagnosis of diabetes insipidus

- Polyuria, variable, 18-20 liter/day in most severe cases.
- Polydipsia.
- Low urinary density (1001-1005 g/cm^3) and urinary osmolality (<200 mosmol/kg).
- Thirst test: DI patients cannot concentrate urine even in case of lack of fluid intake – danger of exsiccosis.
- Oral water and salt test (20 ml/kg water and 0.9 % NaCl) on two consecutive days, in healthy individuals, diuresis after salt test is less than after water intake.
- Urine output decreases after desmopressin administration.

Treatment of central diabetes insipidus

- ADH is not stable for clinical use.
- ADH-analogue desmopressin, DDAVP as nasal spray, or tablets.
- Daily dose 1-2x 1 spray or 3x100-200 µg in tablets
- Other, very rarely used other drugs: clhlorpropamid enhances the tubular action of ADH, carbamazepin stimulates endogenous ADH-secretion.

Nephrogenic diabetes insipidus

- Disorder of renal ADH action.
- Two major forms:
  - Rare congenital (VP2 and AQP2 mutations)
  - Acquired (chronic renal diseases, metabolic disturbances /hypercalcaemia, hypokalaemia, gout/, osmotic diuretics /mannitol/, drugs /lithium, demeclocyclin, vincristin/)
- Treatment:
  - NSAID (indometacine, ibuprofen, aspirin) reduces polyuria, increases osmolality
  - Mild volumen depletion, tiazide diuretics in combination with NSAIDs are effective. K-sparing diuretics (amilorid) + tiazid also effective.

SIADH
Syndrome of inappropriate secretion of antidiuretic hormone.

Major characteristics of paraneoplastic syndromes.

- Hormone secretion is rarely to be inhibited.
- Mostly seen in advanced cancer diseases.
- Hormones are not efficient as tumor markers.
- Paraneoplastic endocrine syndromes are ofen caused by non-classic hormones, but similar mediators.

Major hormones secreted by tumors

- **Mediators inducing hypercalcaemia**
  - **Parathormon like peptide (PTHrP)**
  - **Vitamin D**
  - **Parathyroid hormone**
- **ADH**
- **ACTH**
- **IGF-II**
- **Others: GHRH, kalcitonin, hCG, GH, CRH, erythropoetin, ANP, endothelin, renin, GI hormonok (GIP, somatostatin, PP, VIP etc.)**

Diagnostic criteria of paraneoplstic endocrine syndromes

- **Clinical criteria**
  - 1. hormone secretion is associated with the tumor
  - 2. serum or urinary hormone concentrations are unusually high
  - 3. hormone secretion cannot be inhibited
  - 4. other cause is excluded
  - 5. syndrome can be cured with tumor removal

- **Research criteria**
  - 1. hormone or mRNA of peptide hormones are detected in tumor tissue
  - 2. Hormone is secreted by cell cultures isolated from the tumor
  - 3. A concentration gradient is measured between arterial and venous sides of the tumor.

SIADH

- Probably the second most frequent paraneoplastic syndrome.
- ADH hypersecretion.
- Consequences:
  - Severe hyponatraemia (se Na often <120 mmol/l).
  - Serum hypoosmolality (<275 mOsm/kg), urine is inappropriately concentrated (>100 mOsm/kg) and Na concentration is high.
  - Somnolence, come, seizures in severe cases.

Major causes of SIADH

- Tumors, paraneoplastic syndromes.
- CNS diseases (brain tumors, inflammations)
- Drugs (psychiatric medications /tricyclic antidepressants, phenotiazines)

Major tumors leading to SIADH

- Small cell lung cancer (in 5-15% of patients SIADH can be observed)
- Other lung tumors.
- Carcinoids, prostate cancer., cervix cancer rarely, but many other tumors, as well.

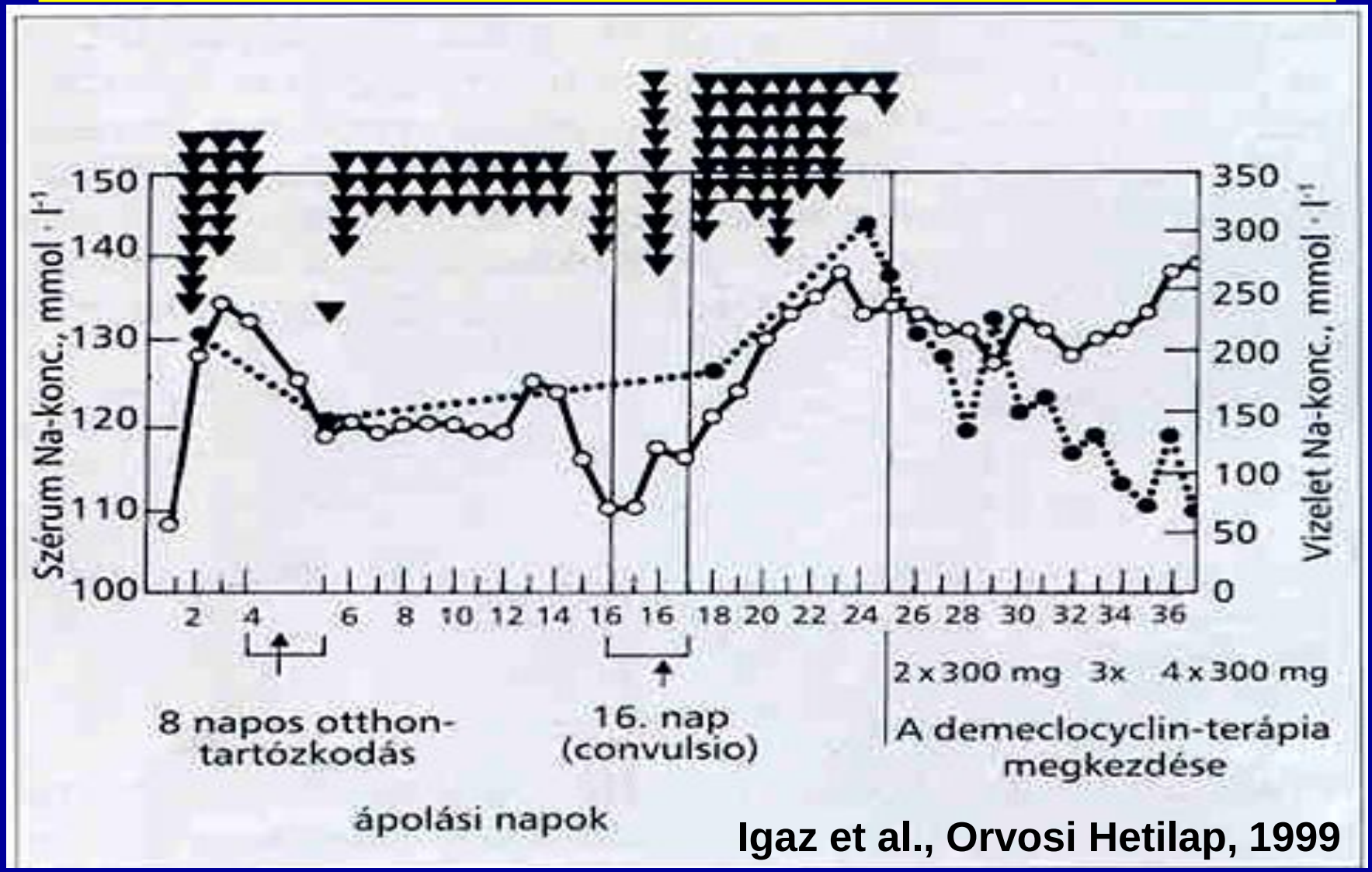
Diagnosis of SIADH

- Hypoosmolar serum, and highly concentrated urine.
- Hyponatremia, high urinary Na-concentration.
- Lack of edemas.
- Other causes excluded: hypothyroidism, Addison-disease, hypopituitarism, drugs (psychiatric drugs, diuretics), CNS diseases.

Treatment of SIADH

- **Severe case (se Na < 120 mmol/l)**
  - Hypertonic salt infusion
  - With or without loop diuretic
  - Target: 125 mmol/l
  - Speed of normalization cannot be higher than 0.5 mmol/l/h-t: danger of central pontine myelinolysis.
- **Milder case (se Na > 120 mmol/l)**
  - Fluid restrictionó (daily intake < 800-1000 ml)
  - Demeclocyclin inhibiting renal ADH action in chronic cases.

Effect of demeclocyclin of serum and urinary Na-concentration in a SIADH patient



Igaz et al., Orvosi Hetilap, 1999