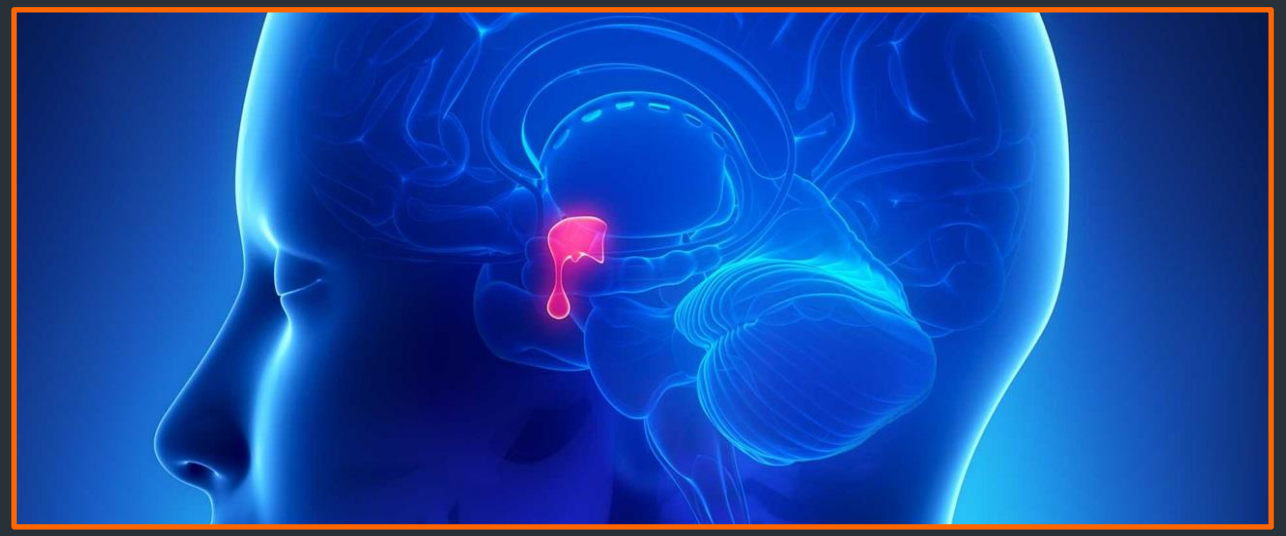
# Clinical heterogeinity of hypothalamic-pituitary dysfunction: on the example of clinical case.



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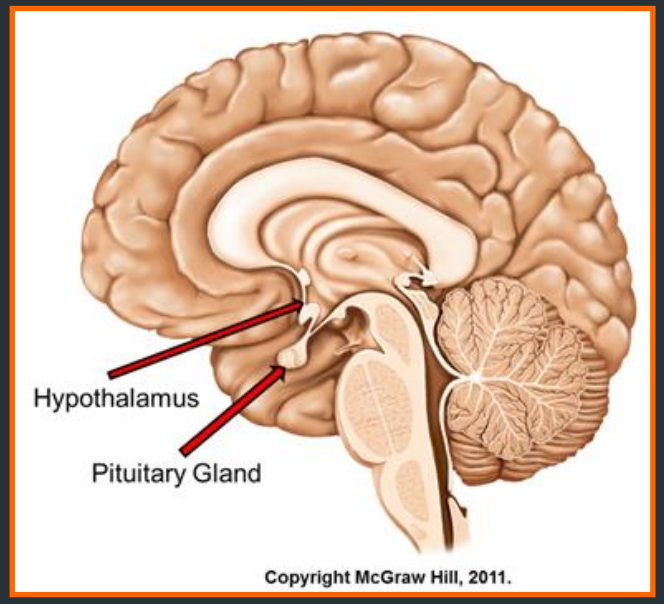
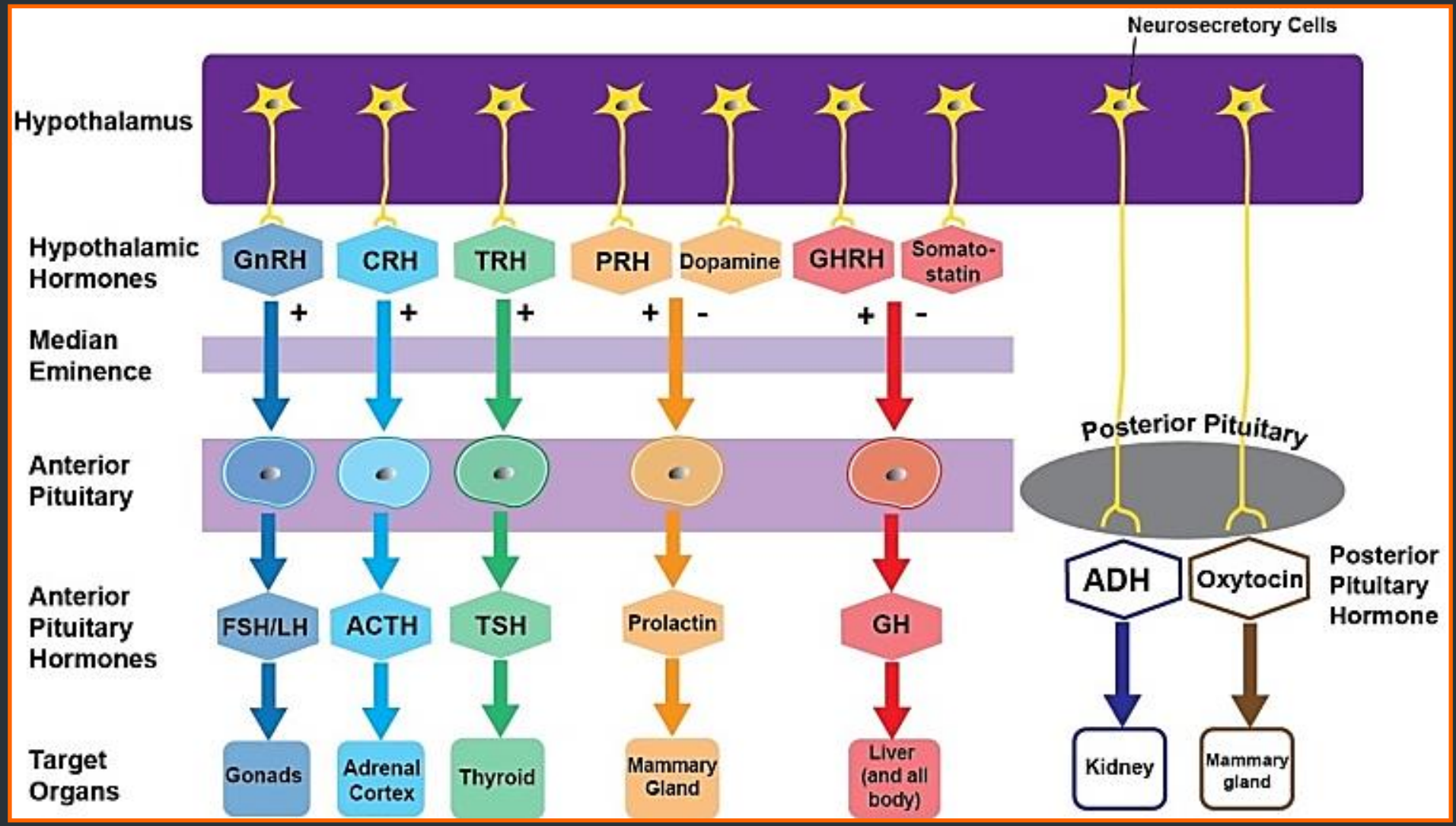
# Introduction

- **Hypothalamic-pituitary dysfunction (HPD)** often has a heterogeneous character, which determines the **presence of various endocrinological comorbidities in one patient** due to the anatomical proximity of the structures of the hypothalamic-pituitary region and the possibility of simultaneous damage of its neighboring areas.




- **Patients with chronic endocrine pathology should be educated** about the characteristics of their disease and cautions in its treatment.
- This clinical case illustrates the variety of clinical features in the patient with HPD and the consequences of insufficient education of the patient about the specific treatment cautions.

# Physiology of hypothalamus and pituitary

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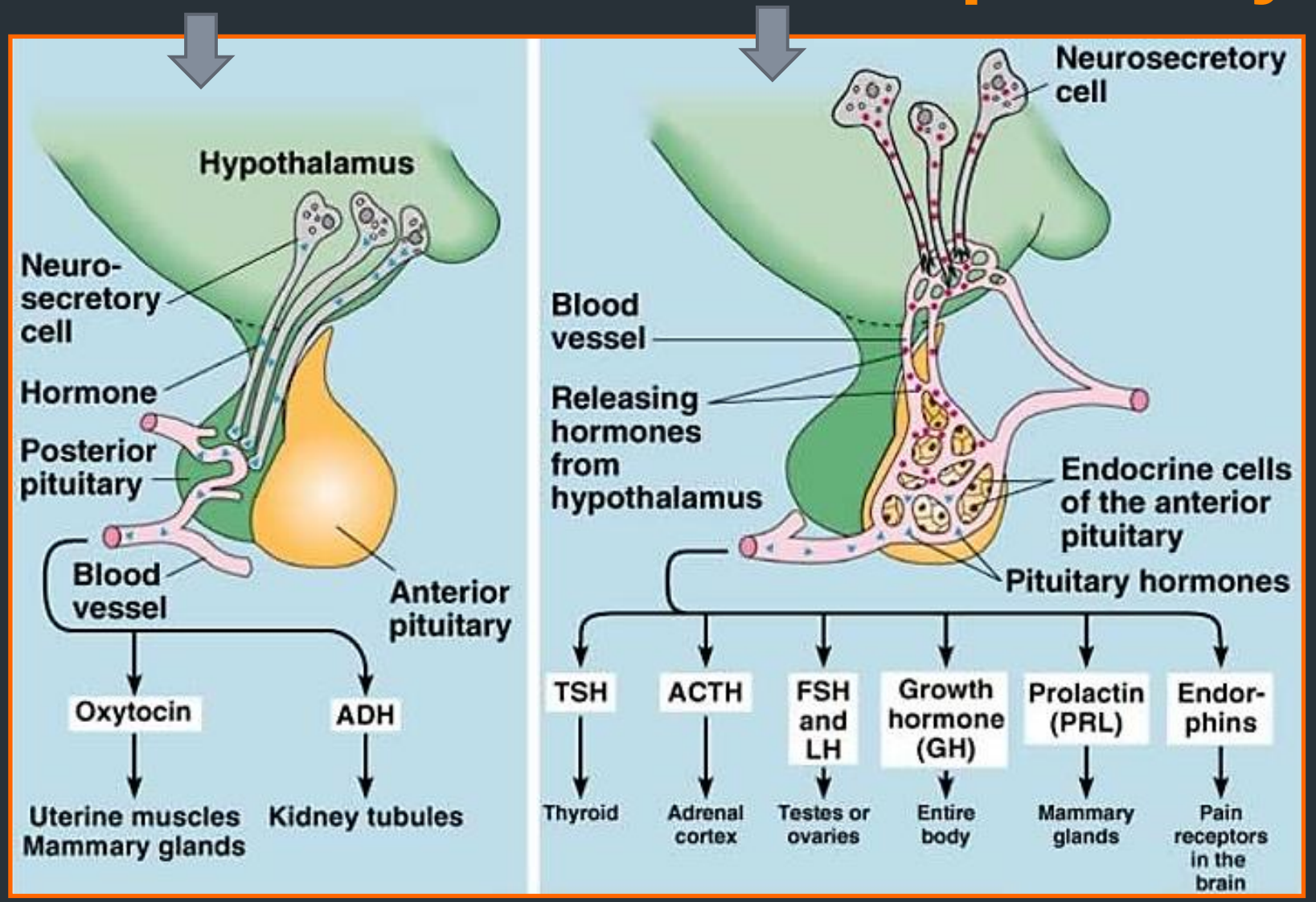
# Posterior and anterior pituitary

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# Diabetes insipidus

**Diabetes insipidus (DI) is defined as the passage of large volumes (>3 L/24 hr) of dilute urine (< 300 mOsm/kg).**

**It is characterized by excessive urination ( 3-20 L/day ) and extreme thirst as a result of:**

- **inadequate output of the pituitary hormone ADH (antidiuretic hormone, also called arginine vasopressin [AVP])**
- **or the lack of the normal response by the kidney to ADH.**


***Diabetes*** **[Greek] =** ***to go through*** **[describing excessive urination]**
**Insipidus [Latin] = without taste**

https://www.sgagora.com.br/sg/wp-content/uploads/2018/05/diabetes-insipidus_22404_l-e1525360806527.jpg

# Facts about DI

- DI is a rare disease, with a prevalence of 1:25,000.
- The US rates of DI are much higher than the rest of the world – 1:6,666.
- Up to 30% of the cases of DI are idiopathic forms without identified cause.
- 1 in 5 people who must undergo a cranial surgery will develop DI during their recovery period.
- The prognosis for patients with DI is generally excellent; DI-related mortality is rare in adults as long as water is available

https://www.zipheal.com/wp-content/uploads/2013/01/diabetes_insipidus_symptoms.jpg

https://diabetesinsipidus.org/diabetes-insipidus-statistics

# Types of DI

- **Central DI - impaired synthesis, transport or osmoregulated secretion of vasopressin;**
- **Nephrogenic DI – due to resistance to ADH action in the kidney;**
- **Gestational DI - rare complication of pregnancy, usually developing in the third trimester and remitting spontaneously 4-6 weeks post-partum.**
- **Primary polydipsia - a syndrome characterized by compulsive fluid intake with physiological inhibition of ADH secretion or dyspsogenic polydipsia with decreased sensitivity threshold of osmoreceptors.**

# Causes of DI-1

## Central DI:

- Genetic defects of ADH synthesis and transport
- Idiopathic (30% of the cases)
- Head trauma or surgery
- Tumors of the hypothalamic-pituitary area
- Vascular causes (Sheehan syndrome, thrombosis, hemorrhage, etc.)
- Infections , autoimmune diseases, etc.

## Nephrogenic DI:

- Genetic mutations (vasopressin V2 receptor gene, aquaporin 2 gene)
- Renal diseases (pyelonephritis, polycystic kidney disease)
- Amyloidosis
- Multiple myeloma
- Sickle cell anemia
- Medications such as lithium

# Causes of DI-2

- **Primary polydipsia (PP)**
- The pathogenesis of PP remains unexplored.
- Different theories include a dysfunction in the thirst mechanism, hippocampus involvement, stress-reducing behaviour, psychiatric disorders (schizophrenia, anxiety disorder, depression)

**Gestational DI**

- It is caused by excessive vasopressinase activity, an enzyme expressed by placental trophoblasts which metabolises AVP.

# Signs and symptoms of DI

- Polyuria (3 to 20 L) with large volumes of diluted urine
- Nocturia and related fatigue from interrupted sleep
- Polydipsia, especially a desire for cold fluids up to 20 L
- Marked dehydration, as evidenced by dry skin and mucous membranes, reduced sweating and salivation
- Low blood pressure
- Anorexia and epigastric fullness, weight loss


https://i.pinimg.com/originals/1a/ac/76/1aac765799f13a3b7f3b51cf6568366a.jpg

# Diagnostics of DI

- A 24-hour urine collection for determination of urine volume (Zimnitskiy test)
- Serum electrolyte concentrations and glucose level
- Urinary specific gravity
- Simultaneous plasma and urinary osmolality
- Plasma ADH level

Additional tests:

- Water deprivation (Miller-Moses) test to ensure adequate dehydration and maximal stimulation of ADH for diagnosis
- Pituitary studies, including magnetic resonance imaging (MRI) and measurement of circulating pituitary hormones other than ADH

# Treatment of central DI

- Dinamic monitoring of water balance (fluid intake and output) Urine osmolality, specific gravity of urine, blood electrolytes (Na, K, Mg, and P )
- Hormone replacement with vasopressin or desmopressin, orally or intranasally. Orally in tablets initial dose of 0.1 mg 2-3 times a day orally 30-40 minutes before meals or 2 hours after meals. Average doses vary from 0.1 mg to 1.6 mg per day. Water consumption should be restricted 1 hour before and during desmopressin therapy. Side effects: hyponatriemia, headaches, face hyperemia, nausea, vomiting
- Rarely used - chlorpropamide, clofibrate, or carbamazepine (to stimulate secretion of ADH or increase release)

# Treatment of nephrogenic DI

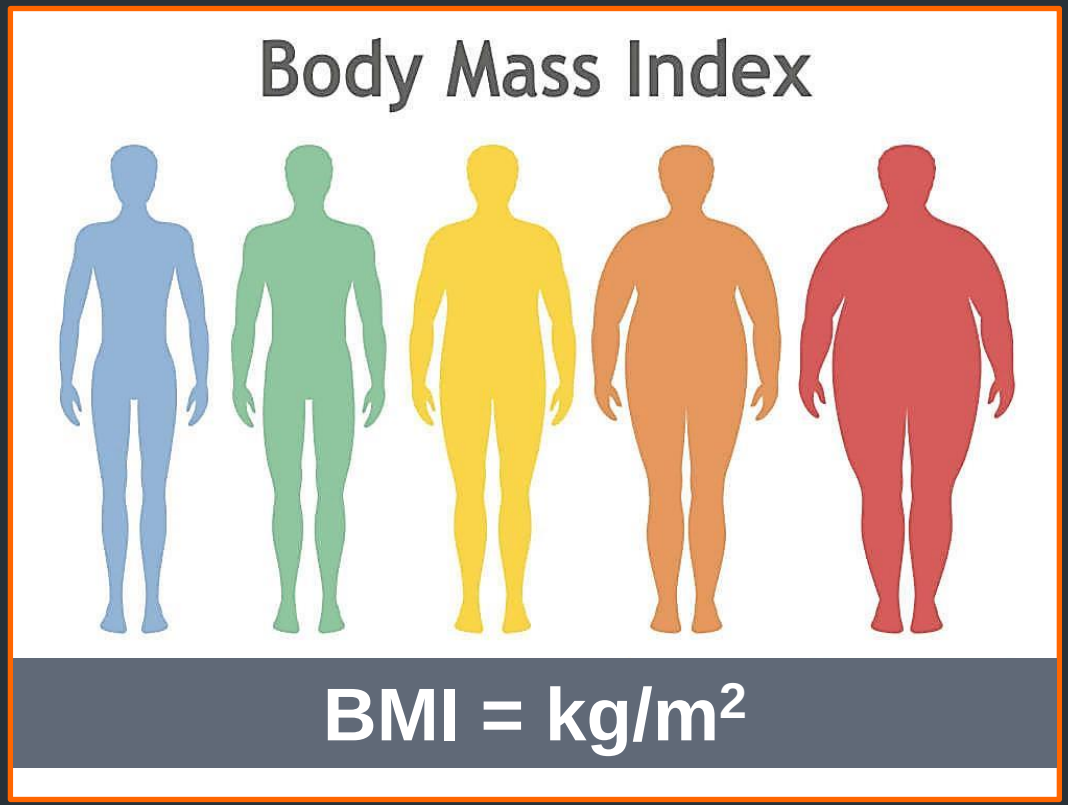
- stopping any causative drug
- monitoring fluid balance, electrolyte levels, supplying I.V fluids
- Na restriction with thiazides (stimulates sodium and water reabsorption in PCT, that decreases water delivery to distal nephron limiting polyuria)
- Amiloride +/- thiazide : especially when Lithium exposure is the cause (amiloride limits lithium entry into tubular cells)
- others:  Indomethacin and ibuprofen, desmopressin (in those with receptor mutations high doses may be useful)

# Treatment of primary polydipsia (PP)

- ingestion of a balanced diet, avoidance of drugs that may cause a dry mouth
- behavioral therapy such as disease education, relaxation training using biofeedback,, group therapy and etc.
- in psychotic patients are used antipsychotic drugs and mood stabilizers such as olanzapine, lithium, risperidone, aripiprazole and clozapine, etc.
- Acute treatment of hyponatraemia in PP primarily consists of fluid restriction. In cases of profound and symptomatic hyponatraemia, a 3% saline infusion may be used
- Desmopressin and diuretics are contraindicated

# Obesity

- **Obesity represents a state of abnormal or excessive storage of body fat that may impair health with BMI (body mass index) greater or equal 30 kg/m² .**




**European Guidelines for Obesity Management in Adults, 2015**

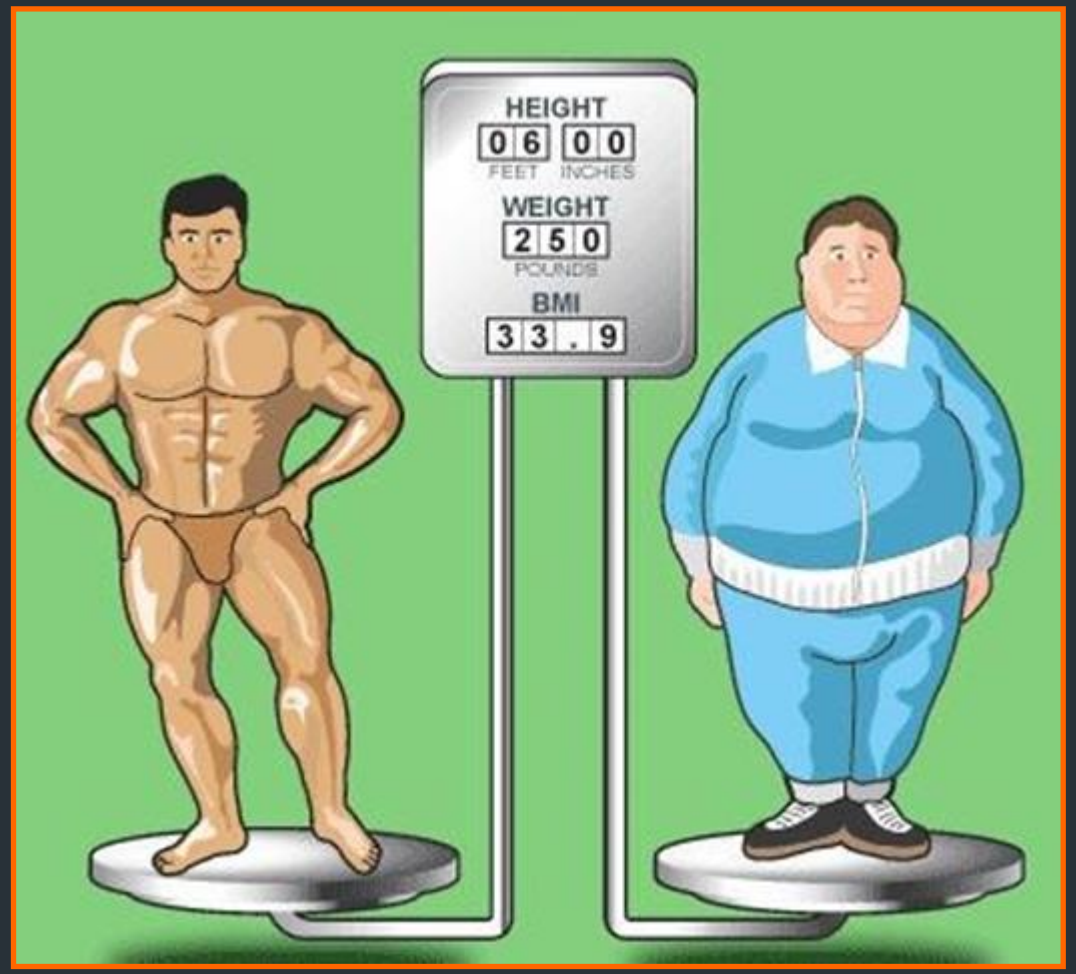
| Category | BMI, kg/m² |
|---|---|
| Underweight | <18.5 |
| Healthy weight | 18.5–24.9 |
| Pre-obese state | 25.0–29.9 |
| Obesity grade I | 30.0–34.9 |
| Obesity grade II | 35.0–39.9 |
| Obesity grade III | ≥40 |

https://thescrutinizer.org/wp-content/uploads/2015/12/BMI-Classification-1.jpg

# BMI measurement considerations

**Limitations to the use of BMI for diagnostic purposes are:**

- **the presence of edematous syndrome, for example, with decompensated heart failure, kidney disease;**
- **errors in the assessment of BMI are possible in athletes due to the significant development of muscle mass**

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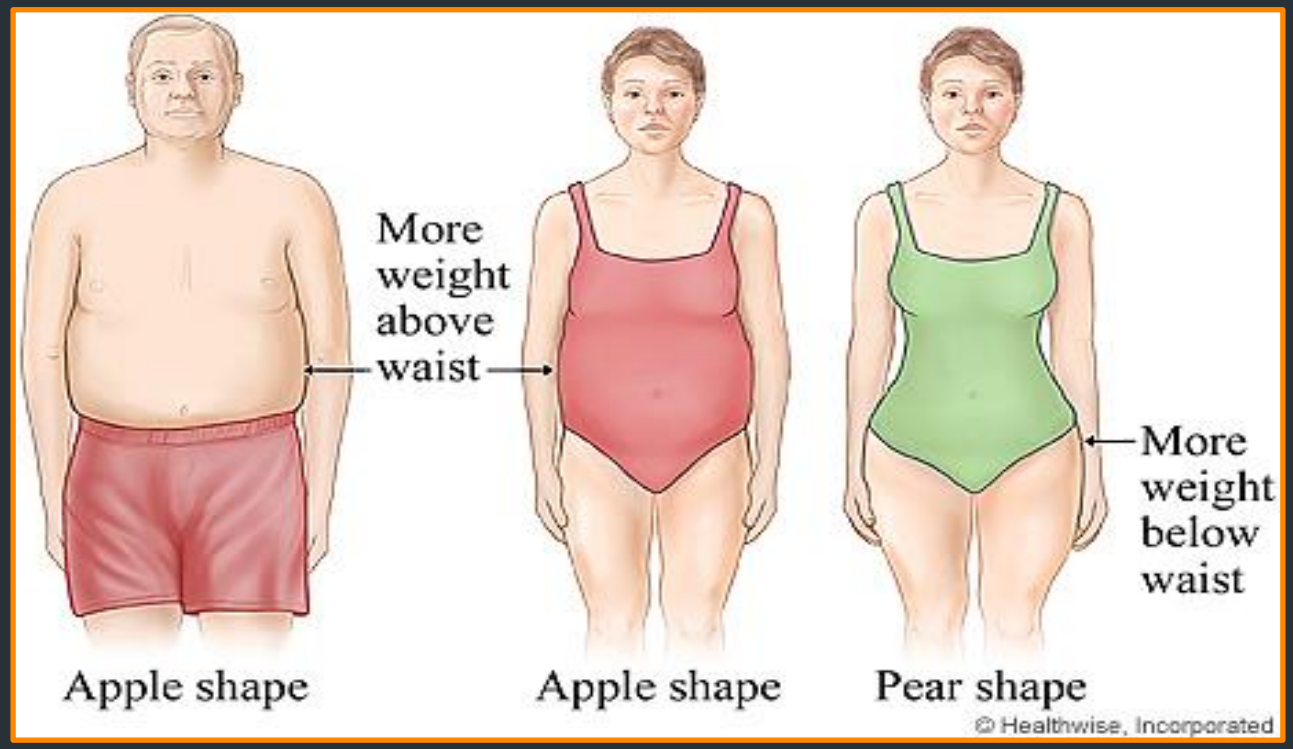
# Fat distribution: gynoid vs android obesity

- **Android:** body fat around the trunk and upper body, in areas such as the abdomen, chest, shoulder and nape of the neck (apple shape).
- **Gynoid:** body fat that forms around the hips, breasts and thighs (pear shape).




Useful tool for the differentiation of these types and fat distribution in obesity is the waist-to-hip ratio (WHR). It is the circumference of the waist divided by that of the hips.

# Morbid obesity

**Morbid obesity - a serious health condition that results from an excessive body mass:**

- **with a body mass index (BMI) > 40 kg/m²,**
- **a BMI > 35 kg/m² with at least one serious obesity-related condition such as type 2 diabetes mellitus, arterial hypertension, etc.,**
- **Weight of the patient is more than 100 pounds over ideal body weight (IBW).**

https://i.imgflip.com/1sfuoi.jpg

# Types of obesity

**Obesity is divided to:**

- **Primary (alimentary constitutional): gynoid and android.**

**Primary obesity is associated with an excessive caloric intake, decreased energy expenditure and/or a combination of the two.**

- **Secondary obesity due to another diseases:**

1. **With an identified genetic defect (i.e. Down syndrome, etc.)**
2. **Cerebral (adipozogenital dystrophy, brain tumors, infectious diseases, disseminated systemic lesions)**
3. **Endocrine (hypothyroid, hypovarian, diseases of the hypothalamic-pituitary system, adrenal gland diseases);**
4. **Iatrogenic (due to drug intake: steroid treatment, etc.)**

# Some types of secondary obesity




https://www.degruyter.com/view/j/jpem.ahead-of-print/jpem-2013-0070/graphic/jpem-2013-0070_fig1.jpg , http://www.scielo.org.za/img/revistas/samj/v106n7/13t3.jpg

# Diagnostics of obesity

- Fasting blood glucose
- Serum lipid profile (total, HDL and LDL cholesterol, triglycerides)
- Uric acid
- Thyroid investigation (thyroid-stimulating hormone (TSH) level, T3, T4, anti-TPO, thyroid ultrasound)
- Cardiovascular assessment, if indicated
- Endocrine evaluation if Cushing's syndrome or hypothalamic disease suspected
- Liver investigation (Liver function tests, ultrasound, biopsy) if abnormal liver function tests suggest NAFLD or other liver pathology
- Sleep laboratory investigation for sleep apnea.

# Management of obesity

- **European Guidelines for Obesity Management in Adults, 2015**


**<u>Management of comorbidities</u>:**
**– management of dyslipidemia,**
**– glycemic control in type 2 DM,**
**– normalizing BP in hypertension,**
**– management of pulmonary disorders (sleep apnoea syndrome),**
**–pain control and mobility needs in osteoarthritis,**
**– management of psychosocial disturbances (affective disorders, eating disorders, low self esteem and body image disturbance).**

# Our patient

- Name: R. T.
- Sex: Male
- Age: 24 Years (1995)
- Location: Kharkiv
- Occupation: Paramedic
- Level of disability: disability from childhood (IIIrd degree)

# Complaints

- **frequent painless urination with the release of a large volume of colorless urine (urinates every 2-3 hours, diuresis 8-10 l / day with a predominance of night diuresis);**
- **thirst (drinks 8-10 l of fluid per day);**
- **weight gain (over the past year has gained 10 kg);**
- **Also complains of periodically occurring diffuse headaches of a expanding nature, dyspnea of mixed character during physical exertion (fast running, climbing to the 4th-5th floor).**

# Anamnesis of present illness -1

- Thirst and urination with passage of large volumes of dilute urine first appeared at age of 3,5 years (was on breastfeeding till 3 years). Was diagnosed with central diabetes insipidus, replacement therapy (desmopressin) was prescribed, against which the patient's condition improved (thirst, diuresis decreased to 3-4 l/day).
- Since 4 years the patient has been gaining weight progressively.
- Patient has planned inpatient treatment in the endocrinology department annually. The last 5 years the patient took desmopressin unsystematically and did not adhere to the water regimen restrictions during drug therapy. When using desmopressin, he also noted the occurrence of a headache, accompanied by nausea.

# Anamnesis of present  illness -2

- In November 2019, the patient stopped treatment, because, in his opinion, “desmopressin increased his weight and caused headaches”.  After this, the patient's condition worsened, diuresis and thirst increased significantly. He referred to endocrinologist for further investigation and correction of therapy.

# Anamnesis of life

- Patient is working as a paramedic;
- Married, has a son;
- Denies alcohol abuse, smoking (stopped smoking in 2018, before had been smoking since 13 years old – 1 pack per day).
- Postponed diseases: upper respiratory viral infections (URVI), postponed operations: denies.
- Tuberculosis, viral hepatitis, HIV, diabetes mellitus, peptic ulcer, allergic reactions denies.
- Hereditary history is not burdened.
- Disability from childhood - IIIrd degree

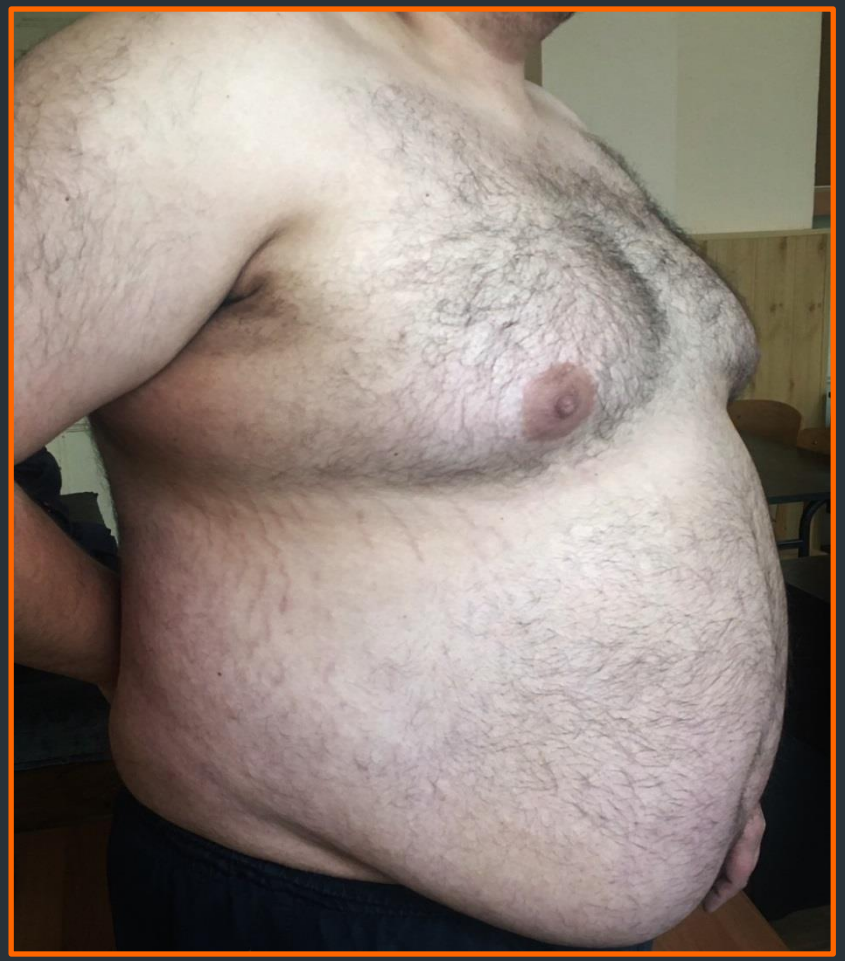
# Objective examination-1

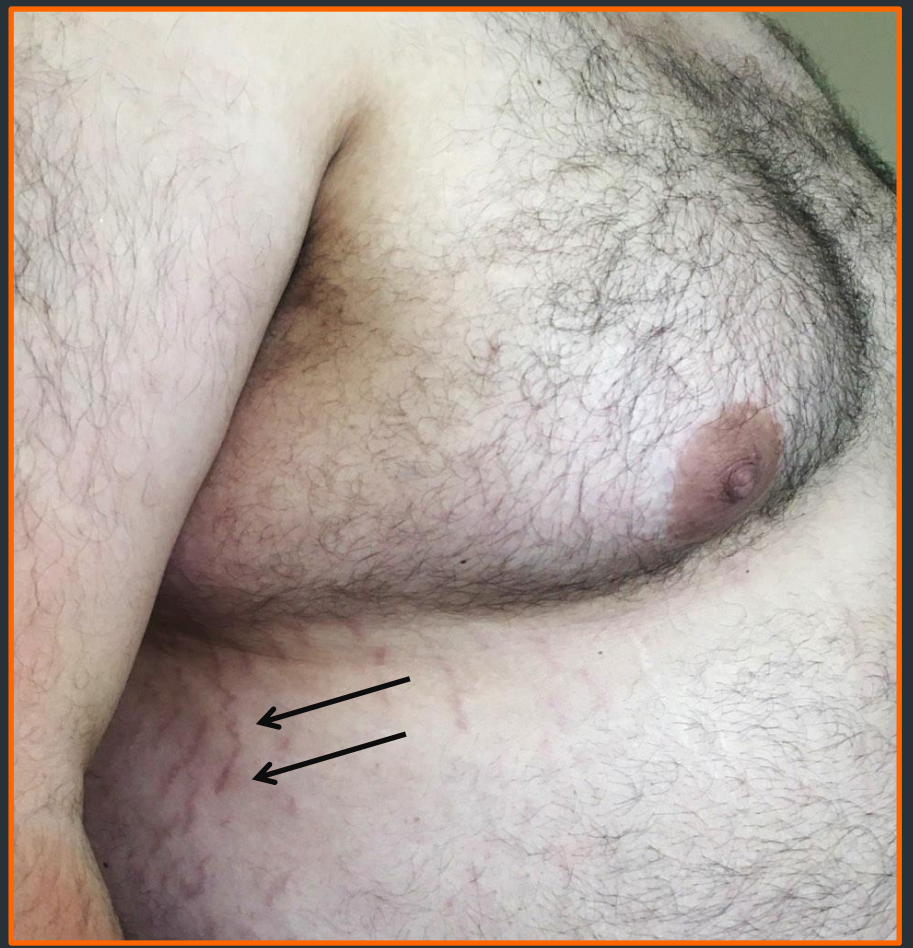
- General condition of the patient is satisfactory.
- Height 1.84m, weight 155kg, BMI-45.8 kg/m$^2$, waist circumference – 146cm, hip circumference – 145cm, waist-to-hip ratio -1.1. T=36,7 C.
- Skin is clean, turgor, moistness is preserved; there are pink striae in the chest area, pale striae in the shoulder area; visible mucous membranes are clean, moist.
- Subcutaneous adipose tissue - developed excessively, more pronounced in the abdomen, chest, back. There is gynecomastia, buffalo hump. Lymphatic nodes - not palpable. No edemas.
- Musculo-sceletal system – without pathological changes.

# Objective examination-2

- Thyroid gland is not enlarged.
- Lungs: resonance percussion sound, vesicular breathing over both lungs fields, RR -18/min.
- Heart borders on percussion are not enlarged, heart tones are clear, muffled, rhythmic; BP dex – 140/95, BP sin – 140/92, HR=pulse - 100 bpm, rhythmic.
- Abdomen is painless on palpation in all regions. Liver is not enlarged ( liver size according to Kurlov: 7-8-9 cm), the spleen is not palpable.
- Tapping sign - negative on both sides. Urination - free, painless, frequent, voluminous (up to 20 times per day).

# Objective status





- Abdominal obesity is present, gynecomastia, purple striae (black arrows)

# Plan of survey

- Full blood count, urinalysis
- Biochemical panel (FPG, OGTT,  lipid profile, CRP, electrolytes, LFT, KFT);
- Insulin level, HOMA index;
- thyroid function tests (T3, T4, TSH, anti-TPO ab), prolactin, cortizol;
- Serological panel (viral hepatitis B, C tests);
- ADH in blood, brain contrast MRI – refused to do tests due to financial issues
- ECG, EchoCG;
- Brain CT, EEG, REG;
- Ultrasound of kidneys, abdominal organs, thyroid gland, breast glands;
- Consultation of endocrinologist, cardiologist, neurologist

# Full blood count

| Options | Results | Normal range |
|---|---|---|
| Hemoglobin, g/L | 145 | 130,0 – 160,0 |
| Erythrocytes × $10^{12}$/l | 4,72 | 3,7-4,7 |
| Color index | 0,92 | 0,85 – 1,15 |
| Leukocytes × $10^{9}$/L | 8,3 | 4,0 – 9,0 |
| ESR, mm/h | 5 | 2-15 |
| Stab neutrophils, % | 1 | 1-6 |
| Segmented neutrophils, % | 54 | 47-72 |
| Eosinophils, % | 2 | 0,5-5,0 |
| Basophils, % | 0 | 1-1,0 |
| Lymphocytes, % | 36 | 19-37 |
| Monocytes, % | 7 | 3-11 |

**Conclusion:** all parameters within the normal range

# Urine analysis

| Options | Results | Normal range |
|---|---|---|
| Amount, ml | 60 | |
| Specific gravity | 1,003 | 1,012-1,024 |
| pH | alkaline | 5,0-7,0 |
| Color | colorless | yellow |
| Transparency | transparent | transparent |
| Protein, g / l | not detected | to 0.033 |
| Glucose | not detected | absent |
| Leucocytes, cells/hpf | 1-2 | 0-6 |
| Epithelium, cells/hpf | 0 | absent |
| Bacteria | Not detected | absent |

**Conclusion:** decreased urine specific gravity

# Zimnitskiy test

| Options | Results | | |
|---|---|---|---|
| Diuresis during 24 hours | 6.00-9.00 a.m. | 1000 ml | |
| | 9.00 -12.00 | 1300 ml | |
| | 12.00 - 3.00 p.m. | 1750 ml | |
| | 3.00 - 6.00 p.m. | 2050 ml | |
| | 6.00 – 9.00 p.m. | 2600 ml | |
| | 9.00 – 0.00 | 1900 ml | |
| | 0.00 – 3.00 a.m. | 2000 ml | |
| | 3.00 – 6.00 a.m. | 800 ml | |
| Total diuresis, ml | 13400 ml | Day diuresis 6100 ml | Night diuresis 7300 ml |
| Min specific gravity | 1000 | Max specific gravity | 1003 |

**Conclusion:** decreased urine specific gravity during 24 hours, increased diuresis, nocturia

# Biochemical panel ()

| Options | Results | Normal range |
|---|---|---|
| Total billirubin, mkmol/l | 9,0 | 5-21 |
| Direct billirubin, mkmol/l | 3,0 | 2,2-5,3 |
| Undirect billirubin, mkmol/l | 6,0 | 6,5-15,4 |
| ALT, U/l | 101,9 | <40 (men) |
| AST, U/l | 37,1 | <38 (men) |
| Urea, mmol/l | 4,8 | 1,7-8,3 |
| Creatinine, mkmol/l | 100 | 62-123 |
| CRP, mg/l | negative | <5 |

**Conclusion:** increased level of ALT

# Biochemical panel

| Options | Results | Normal range |
|---|---|---|
| Serum Ca, mmol/l | 2,2 | 2,2-2,5 |
| Serum Fe, mkmol/l | 18,4 | 9,0-29 |
| Serum P, mmol/l | 1,0 | 0,8-1,4 |
| Serum K, mmol/ml | 4,52 | 3,5-5,0 |
| Serum Cl, mmol/l | 100 | 98-106 |
| Serum Na, mmol/l | 142 | 136-145 |
| Alkaline phosphatase, nmol/l | 2200 | 1200-6300 |
| Serum osmolality, mosm/kg | 303,06 | |
| Urine osmolality, mosm/kg | 99,90 | |

**Conclusion:** increased serum osmolality, decreased urine osmolarity

# Biochemical panel - lipid profile

| Options | Results | Normal range |
|---|---|---|
| Total cholesterol, mmol/l | 6,69 | < 5,2 (5,2-6,2 borderline level) |
| Very low-density lipoprotein cholesterol (VLDL-C), mmol/l | 2,86 | 0,26-1,0 |
| Low-density lipoprotein cholesterol (LDL-C) ), mmol/l | 2,93 | <4,12 |
| High-density lipoprotein cholesterol (HDL-C) ), mmol/l | 1,28 | >0,9 |
| Triglycerides), mmol/l | 6,29 | <2,3 |
| Atherogenic coefficient | 6,43 | 2,5-3,0 |

**Conclusion:** increased level of total cholesterol, VLDL, triglycerides, atherogenic coefficient

# Biochemical panel

| Options | Results | Normal range |
|---|---|---|
| FPG (fasting plasma glucose), mmol/l | 5,22 | 4,0-6,1 |
| OGTT (oral glucose tolerance test), mmol/l | 5,22 – 7,1 – 4,2 | Fasting - 4,0-6,1<br>After 2 hours - <7,8 |
| Insulin, | 30,99 | 2,6-24,9 |
| HOMA index | 7,19 | <3,0 |

**Conclusion:** increased level of insulin, HOMA index

# Biochemical panel

| Options | Results | Normal range |
|---|---|---|
| Prolactin, ng/ml | 15,5 | 2,5-17,0 |
| Cortisol, nmol/l | 475 | 138-690 |
| TSH, mcME/ml | 0,946 | 0,27-4,2 |
| Free T3, pg/ml | 3,15 | 2,0-4,4 |
| Free T4, ng/dl | 0,975 | 0,89-1,76 |
| Anti-TPO antibodies, U/ml | 16,9 | <30,0 |

**Conclusion:** all parameters within the normal range

# Serological panel

| Options | Results | Normal range |
|---|---|---|
| Hepatitis B virus, HBsAG | 0,031 | <0,192 |
| Hepatitis C virus, anti-HCV total | 0,034 | <0,222 |

**Conclusion:** all parameters within the normal range

# Instrumental investigations-1

- X-ray of the skull: signs of intracranial hypertension, turkish saddle without pathological changes.
- EEG: moderate diffuse changes of an irritative nature.
- REG: changes of the dystonic type. Obstructed venous outflow.
- CT scan of the brain: convexital subarachnoid spaces without pathological features. Slightly dilated lateral ventricles. Middle structures are not biased. In the anteroposterior area on the right there is an arachnoid cyst up to 11.1 x 8.4 x 20 mm. Pathological foci in the substance of the brain were not identified.
- EchoCG: chambers of the heart are not enlarged, myocardial contractility is satisfactory, ejection fraction – 62%.

# Instrumental investigations-2

- Ultrasound of the thyroid gland. The thyroid gland is not enlarged, located in a typical place, without pathological changes.
- Ultrasound of the kidneys. The kidneys are located typically, of normal shape and size. The parenchyma is not thinned, pyelocaliceal system is not expanded, no pathological changes.
- Ultrasound of the breast glands: the structure of the breast glands is of a fatty type. No areas of glandular hyperplasia were detected. The ducts are not expanded. Pathological masses in the structure of the breast glands were not detected.
- Ultrasound od the abdominal organs: liver is not enlarged, signs of adiposis of the liver. Spleen, pancreas, gall bladder without pathological changes.

# ECG

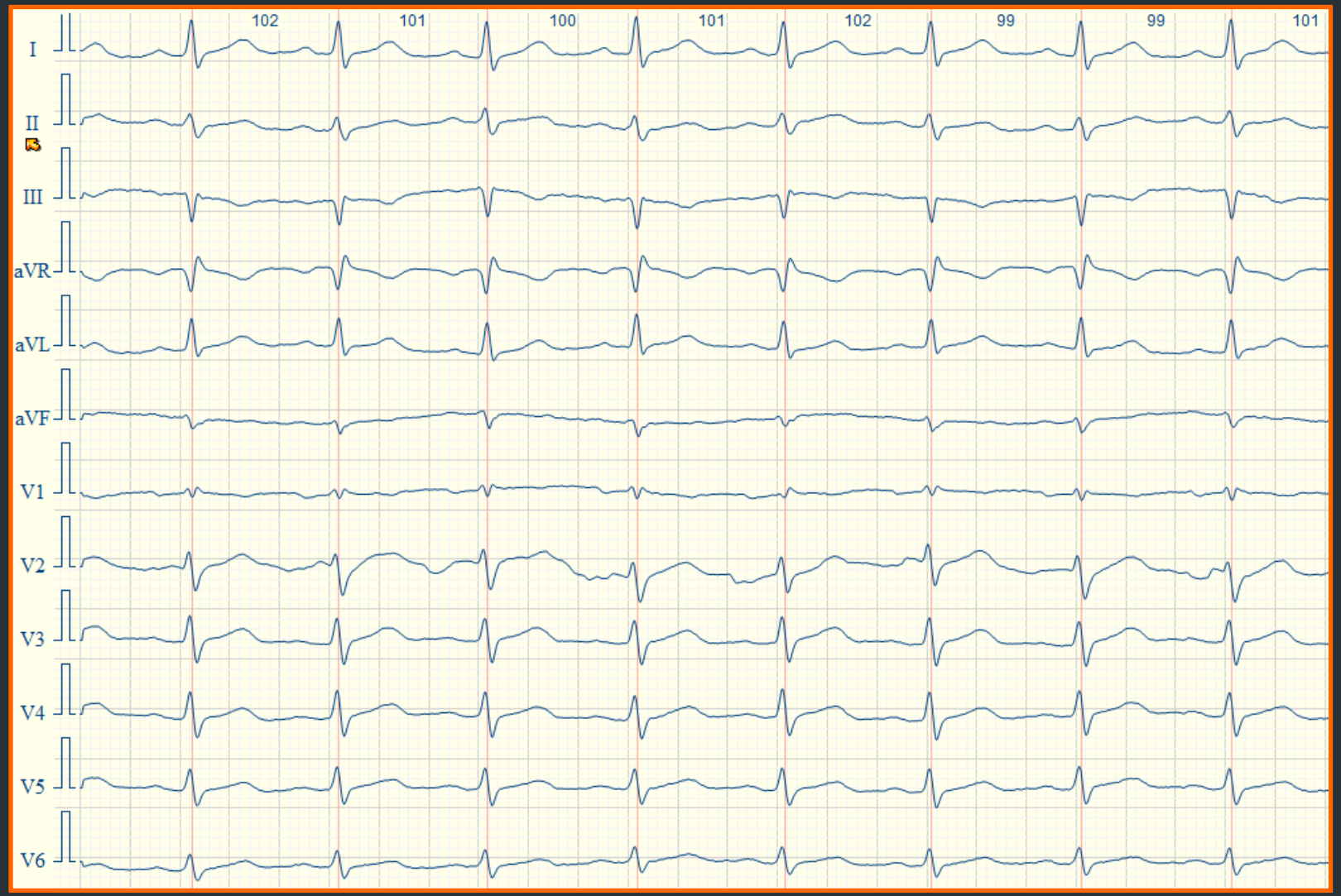
**Conclusion:**

**sinus tachycardia, HR-100,**

**Left axis deviation**

**(aF QRS = -30), left anterior bundle brunch block,**

**Incomplete RBBB, reduction of repolarization processes along the anterior-lateral wall of the left ventricle**



# Consultations of specialists-1

- **Consultation of endocrinologist:** Hypothalamic-pituitary dysfunction with metabolic and endocrine disorders in the form of central diabetes insipidus of moderate severity, obesity of III degree, arterial hypertension of 1st degree, I stage; cerebrospinal venous hypertension, striatal syndrome. Non-alcoholic steatohepatosis.

Recommended: Diet with restriction of satured fat, fast absorbed carbohydrates; food intake 5-6 times per day in small portions.

Desmopressin (uropres) in a starting dose – 5 mcg intranasally with subsequent uptitrating the dose; decrease fluid intake 1 hour before and during use of desmopressin.

**Consultation of neurologist:** discirculatory-dysmetabolic encephalopathy II stage with cerebrospinal venous hypertension.

# Consultations of specialists-2

- **Consultation of cardiologist:** arterial hypertension of I stage, 1 grade, HF0, high cardiovascular risk. Recommended: lifestyle modification (diet with restriction of salt, saturated fat; physical activity), bisoprolol – 5mg once daily under control of HR, BP. Administration of statins is recommended after normalization of LFT levels.
- **Consult of gastroenterologist:** Nonalcoholic hepatic steatosis. Recommended: diet, ademetionin 500 mg twice daily 1 month with subsequent control of LFT.

# Differential diagnosis of DI types

| Criteria | Central DI | Nephrogenic DI | Dipsogenic DI | Our patient |
|---|---|---|---|---|
| Urine specific gravity | <1005 | <1005 | <1010 | 1000-1003 |
| Plasma osmolality | >290 | >290 | <280 | 303,3 |
| Urine osmolality | <200 | <200 | <300 | 99,90 |
| Sodium in blood | ↑ | N | ↓ | 142 |
| ADH in blood | ↓ | ↑ | ↓ | Test wasn't performed |
| Desmopressin treatment effect | + | - | ++ | + (diuresis decreased to 3-4 l/day) |

# Diagnosis

- **<u>Diagnosis:</u> Hypothalamic-pituitary dysfunction with metabolic and endocrine disorders in the form of central diabetes insipidus of moderate severity, obesity of III degree, arterial hypertension of I stage, 1 grade, HF0, high cardiovascular risk; striatal syndrome. Discirculatory-dysmetabolic encephalopathy II st. with cerebrospinal venous hypertension. Arachnoid cyst of the right frontal posterior region. Nonalcoholic hepatic steatosis.**

# Treatment recommendations -1

**Lifestyle recommendations:**

- **Diet with restriction of satured fat, fast absorbed carbohydrates, salt; food intake 5-6 times per day in small portions.**
- **Physical activity (FA) of a dynamic nature, moderate intensity, starting with minimal loads with a gradual increase in the intensity.**

# Treatment recommendation -2

- Desmopressin (uropres) in a starting dose – 5 mcg intranasally with subsequent uptitrating the dose; decrease fluid intake 1 hour before and during use of desmopressin.
- Bisoprolol – 5mg once daily under control of HR, BP.
- Ademetionin 500 mg twice daily 1 month with subsequent control of LFT.
- Administration of statins is recommended after normalization of LFT levels.
- Dynamic observation of endocrinologist, neurologist, neurosurgeon, cardiologist, gastroenterologist.

# Conclusion

- HPD is accompanied by a variety of clinical manifestations, and the components of HPD form a vicious circle, exacerbating each other.
- HPD in this patient manifested as central diabetes insipidus in combination with metabolic syndrome (morbid obesity, dyslipidemia, arterial hypertension, insulin resistance).
- The patient's lack of awareness of the specific features of diabetes insipidus treatment led to the appearance of the side effects, worsening of the general condition and self-cancellation of desmopressin.
- Thus, informing and education of patients about the characteristics of their disease and cautions in drug intake is important for the achieving of effectiveness in the endocrine pathology treatment.

**Thank you for your attention!**
**Any questions?**