Case History of
Familial Combined Hyperlipoproteinemia

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Introduction

Lipid disorders encompass a broad spectrum of metabolic conditions that affect blood lipid levels

They are generally characterized by elevated levels of cholesterol, triglycerides, and/or lipoproteins in the blood in association with an increased risk of (or current) cardiovascular disease

Dyslipidemia
Incidence

29.3% - 53% of adults have dyslipidemia

The majority of lipid disorders are acquired through unhealthy lifestyles (obesity, inactivity, alcoholism, etc)

Hereditary (familial) causes are less common

Fredrickson Classification of Familial Hyperlipidemia

Familial Hyperchylomicronemia

Familial Hypercholesterolemia

Familial Combined Hyperlipoproteinemia

Dysbetalipoproteinemia

Primary Hypertriglyceridemia

Mixed Hypertriglyceridemia

Type	Serum Elevation	Lipoprotein Elevation
I	Cholesterol and triglycerides	Chylomicrons
IIa	Cholesterol	LDL
IIb	Cholesterol and triglycerides	LDL, VLDL
III	Cholesterol and triglycerides	IDL
IV	Triglycerides	VLDL
V	Cholesterol and triglycerides	VLDL, chylomicrons

IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.

Relative Prevalence of Familial Forms of Hyperlipoproteinemia
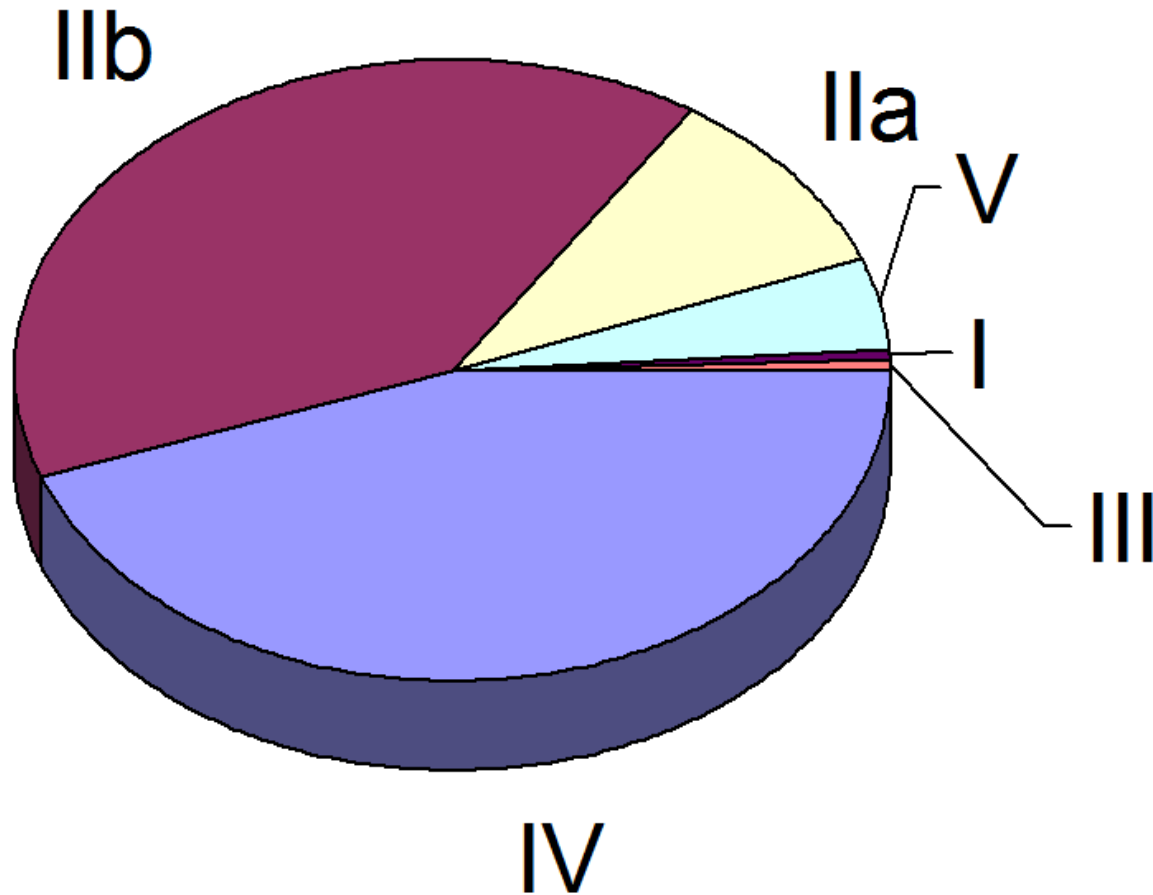
Aquired (Secondary) Dyslipidemia Causes

- Uncontrolled type 1 or type 2 diabetes mellitus
- Endocrine disorders: metabolic syndrome, hypothyroidism, hypercortisolism
- Medications: steroids, estrogen, second generation antipsychotic, antidepressants, accutane, thiazolidinediones, thiazides, beta-blockers, bile acid sequesterants, immunodepressents (sirolimus), antiretroviral therapy
- Pregnancy
- Renal disease: nephrotic syndrome, renal failure
- Liver disease: chronic hepatitis with fatty liver
- Excessive alcohol intake

Purpose

Herein we discuss the clinical case of familial combined hyperlipidemia, a highly atherogenic disorder, that leads obviously to premature disability and to early mortality

Patient B.

43 years old

Complaints

- Retrosternal squeezing, burning pain, radiated to the left arm and left part of the neck, provoked by minimal physical activity (e.g. household chores), sometimes at rest, required nitroglycerin intake (up to 10 td), diminished effect of nitroglycerin

- Palpitations

- Irregular heart beats

- Dyspnea, provoked by walking ground level up to 100 m

- Lower extremities and face edema

History of Presenting Complains

- He feels sick since 2009, when at first episodic blood pressure elevations were occurred (max 180/120 mm Hg, usual 130/90 mm Hg)
- 2014 STEMI of LV inferior wall
- 2015 recurrent STEMI of LV anterior wall, septum, and apex
- 2015 the patient was recommended an angiography, PCI with implantation of drug-eluting coronary stent; due to economic reasons, the patient had refused this procedure
- 2017 hypertensive urgency, BP 180/120mm Hg
- Regular (3-4 times per year) receive in-patient treatment with some positive dynamics; however, despite of regular out-patient medication intake, the therapy effect is not lasting
- Current deterioration occurred during last month: dyspnea was progressed, angina pain developed more often, physical tolerance decreased, effect of nitroglycerin diminished
- The patient was hospitalized to the clinic

Past Medical History

- Since 2005 DM type 2, insulin dependent, severe course, decompensation

FPG 13-17 mmol/L

February 2018: diabetic foot, conservative treatment

- February 2018: community acquired pneumonia in lower lobe of right lung, protracted course

Drug History

- Bisoprolol 5 mg od
- Ramipril 5 mg od
- Atorvastatin 80 mg od
- Aspirin 75 mg od
- Clopidogrel 75 mg od
- Toracemide 5 mg od
- Insulin glargine 20 IU 2 td 8-00, 20-00
- Insulin regular human 10 IU 3 td before meal

Alcohol and Smoking

- The patient denies alcohol consumption

- At present the patient does not smoke (since 2015)
- Before the patient smoked

2 packs per day during 20 years = 40 pack-years

Family History
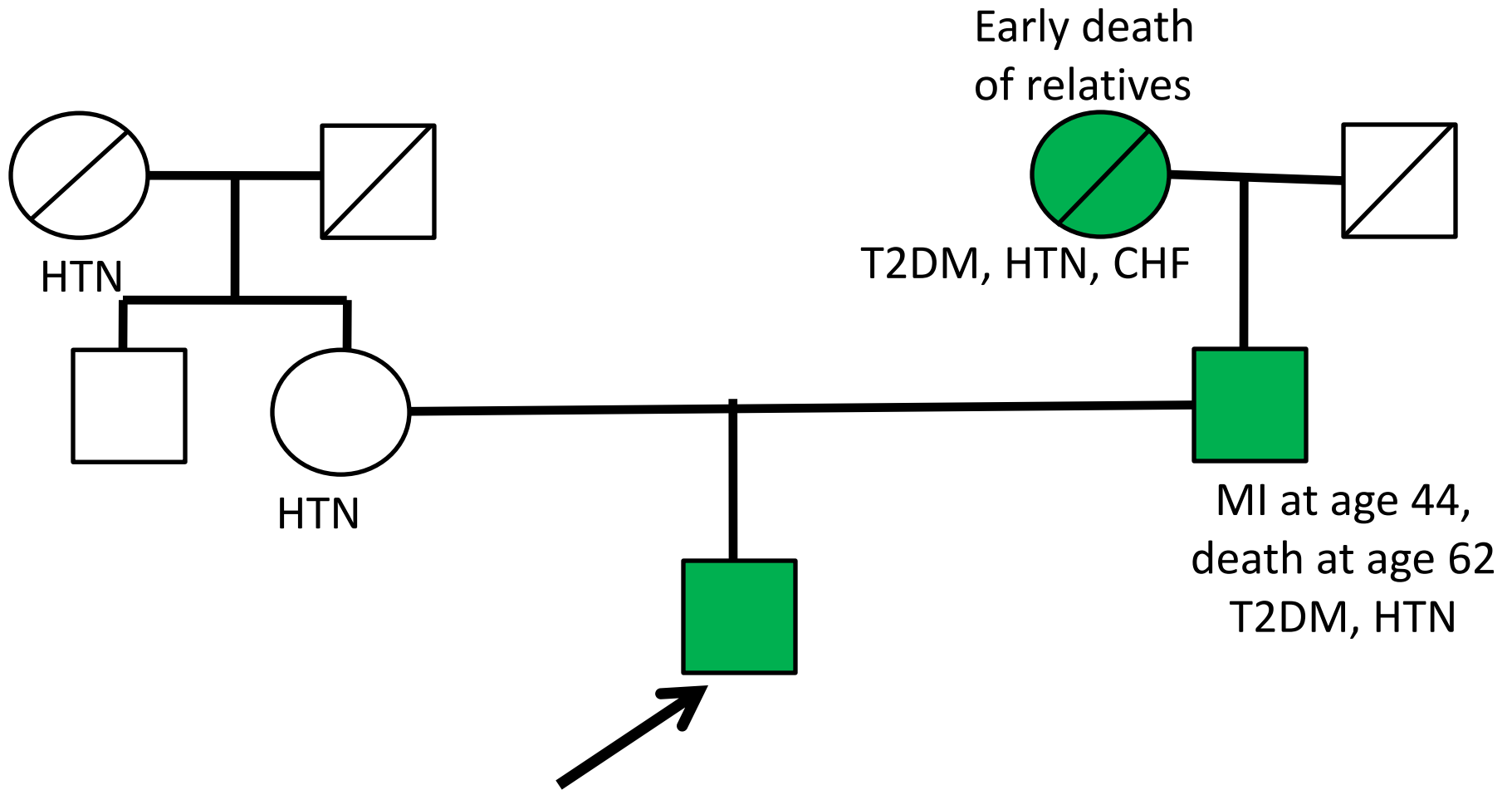
HTN – essential hypertension, T2DM – type 2 diabetes mellitus, CHF – congestive heart failure

Social History

- Worked as a train driver assistant
- Now he is working as a watchman
- Lives in a flat, with his mother
- Has no children

Vital Signs

- T   36, 4°C
- PS   78 bpm
- BP   130/80 mm Hg
- RR   17 tpm
- Height   183 cm
- Weight   120 kg
- BMI   35.8 kg/m²

Examination

Middle aged male, looks older than the passport age, slightly depressive

He is well oriented to space and time

The posture is active

Central type of obesity (waist circumference 146 cm, hips 119 cm, waist/hip = 1.23)

Skin is pink, on eyelids – xanthomas, trunk and extremities – multiple eruptive xanthomas

Visible changes of the neck shape are not detected

Thyroid is palpable, in the left lobe a node ≈1 cmØ is detected

Examination

Bronchial breathing in lungs to auscultation, diminished on basal parts of both lungs

Peripheral pulses is weak, regular

Apex beat is in 5th intercostal space 2 cm to the left of the left midclavicular line, 3 cm², weak

Soft S1 on apex and loud A2 heart sounds to auscultation, diffuse systolic murmur (grade II) at all points

Abdomen is increased in size, participate in breathing actively; during palpation is soft and nontender

Liver is enlarged (+3 cm), soft, nontender to palpation

Spleen is not palpated

Edema of the lower ½ of shins, foots

Nocturia 1-2 per night

Stool is regular, formed

Work up

- Complete blood count
- Urine analisis
- Biochemical blood profile: Liver function tests,
  Kidney function tests,
  Cholesterol profile,
  Thyroid function tests
- B-NP, C-RP
- ECG
- Chest X-ray
- Echocardiography, carotid US
- Abdomen ultrasound
- Thyroid ultrasound
- Genetic counseling

Complete Blood Count

	Results		Reference range	
RBC	5.03 10^{12}/L		3.7-4.7 10^{12}/L	
Hb	162 g/L		130-160 g/L	
WBC	6.0 10^9/L		4.0-9.0 10^9/L	
Neutr Bands	2%	0.1 10^9/L	1-6%	0.0-0.2
Neutr Segmented	54%	3.3 10^9/L	47,0-72%	1.7-7.7
Eosinophils	3%	0.1 10^9/L	0,5-5,0%	0.0-0.6
Basophils	1%	0.1 10^9/L	0,0-1,0%	0.0-0.2
Lymphocytes	34%	2.1 10^9/L	19,0-37,0%	0.4-4.4
Monocytes	6%	0.4 10^9/L	3,0-10,0%	0.0-0.8
Thrombocytes	170 10^9/L		180-320 10^9/L	
ESR	17 mm/h		1-10mm/h	
HCT	42.6%		40-48%	

Urine Analysis

	Results	Reference range
Colour	Yellow	
Specific gravity	1.016	1.001-1.040
pH	6.0	5.0-7.0
Protein	traces	--
Glucose	170 mmol/L	--
Ketone bodies	--	
Leucocytes	1-2 /hpf	6-8/hpf
Erithrocytes	0-1 /hpf	single
Transitional epithelium	single	single
Casts	--	--
Crystals	--	--

Glucose

	Results	Reference range
FPG (capillar)	16.6 mmol/L	3.3-5.5 mmol/L
	16.1 mmol/L	
	16.2 mmol/L	
HB A1c, %	11.9 %	<6,5 %

Glycemic Profile

	9-00	13-00	17-00	21-00	6-00
PG	16.1 mmol/L	16.73 mmol/L	16.14 mmol/L	16.46 mmol/L	15.9 mmol/L

Liver Function Tests

	Results	Reference range
AlAT	16.3 U/L	<33.0
AsAT	3.0 U/L	<32.0 U/L
Bilirubin total **direct** **indirect**	9.8 mkmol/L 3.1 mkmol/L 6.7 mkmol/L	17-21 mkmol/L <5.0 mkmol/L
AP	75 U/L	35-104 U/L
LDH	156.53 U/L	135.0-214.0U/L

Kidney Function Tests

	Results	Reference range
Creatinine	87 µmol/L	62-106 µmol/L
Urea	5.33 mmol/L	3.2-7.3 mmol/L
Potassium	3.8 mmol/L	3.5-5.1mmol/L
Sodium	141.3 mmol/L	136.0-145.0 mmol/L
Chloride	102.4 mmol/L	98.0-107.0 mmol/L

GFR **87.9 mL/min/1.73 m²**
by the MDRD Equation

Cholesterol Profile

|	Results	Reference range
Total cholesterol	17.75 mmol/L*	≤ 5.2 mmol/L
VLDL	3.41 mmol/L	< 1 mmol/L
LDL	13.64 mmol/L	< 3.5 mmol/L
HDL	0.7 mmol/L	> 0.9 mmol/L
Triglycerides	71.35 mmol/L*	< 2.3 mmol/L
Cholesterol/HDL ratio	17.57 mmol/L	< 3.0 mmol/L

min TC, achieved by statin treatment 12.29 mmol/L

**min TG, achieved by treatment 41.48 mmol/L*
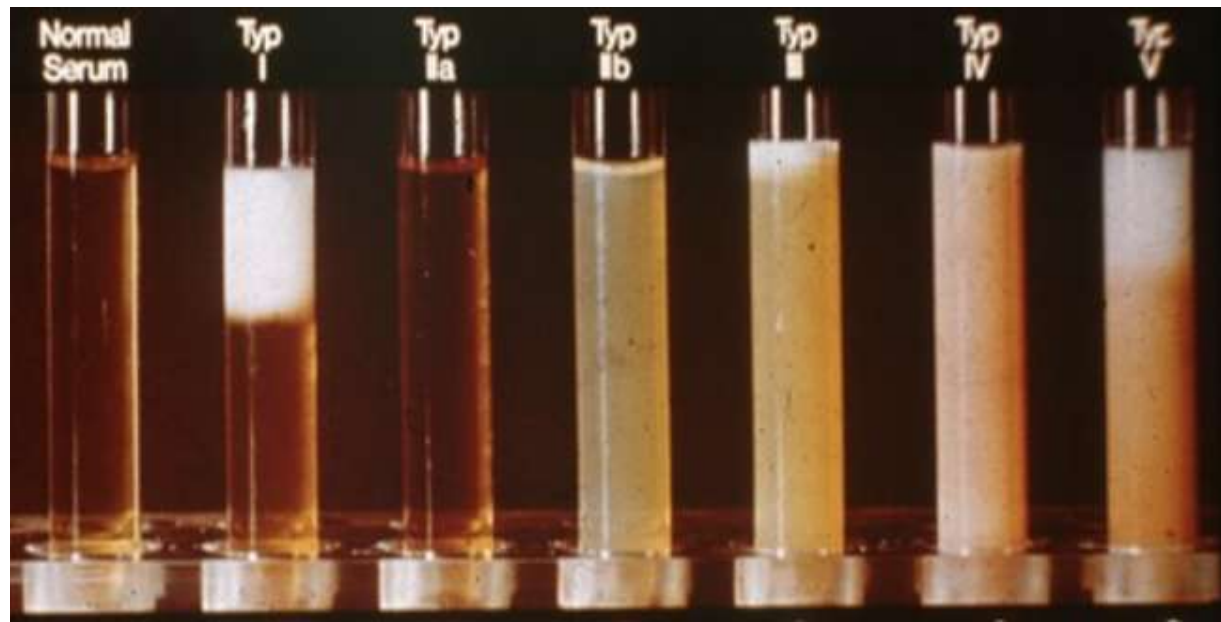
Thyroid Function Tests

	Results	Reference range
TTG	9.92 mg/dL	4.6-14.1 mg/dL
T4	0.675 μIU/mL	0.270-4.20 μIU/mL

ECG
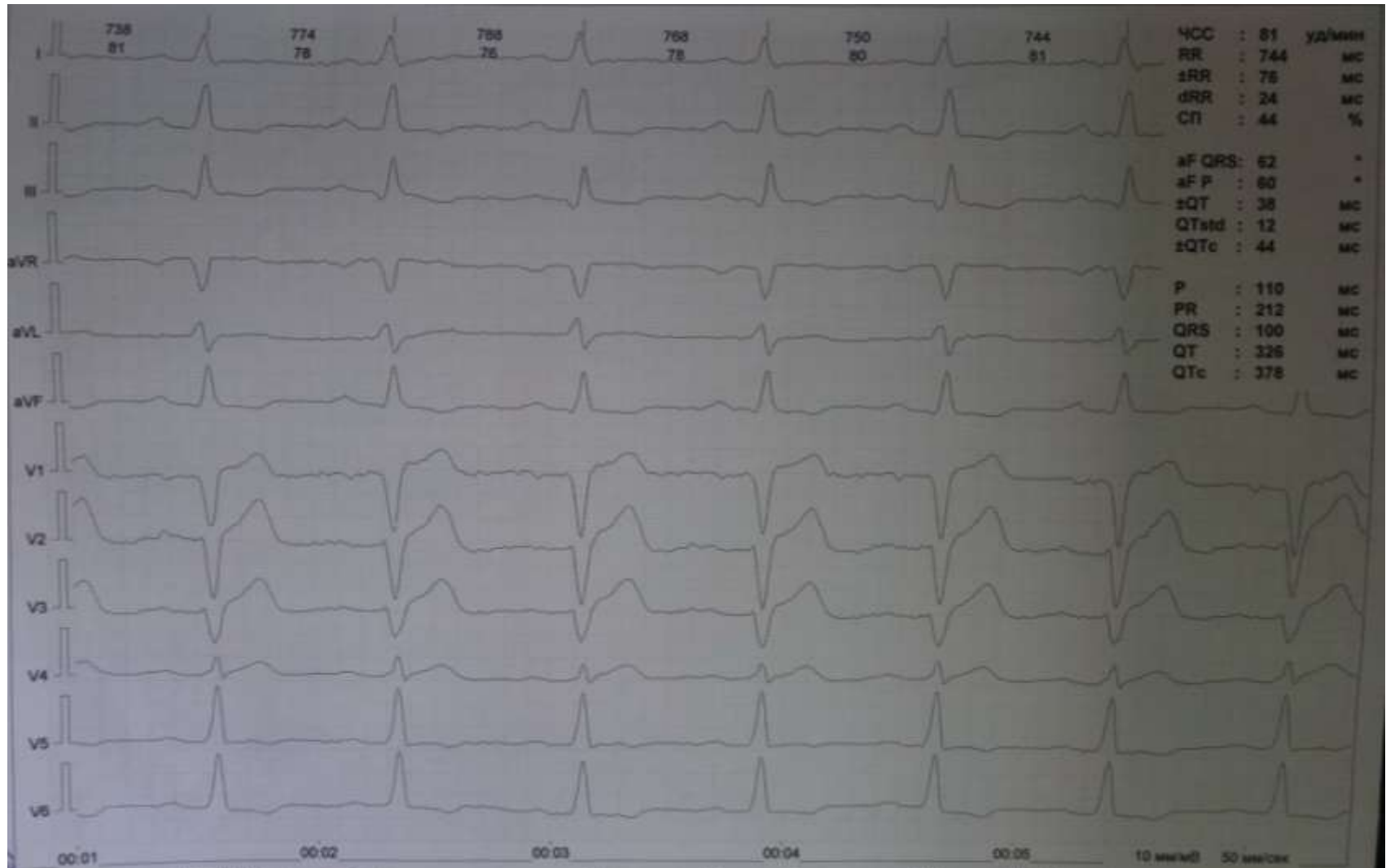
Sinus rhythm, regular, postinfarction cardiosclerosis (anterior, posterior wall, apex), violation of repolarisation

Transthoracic Echocardiography

- Sclerotic changes of aorta, aortic and mitral valves
- Dilation of all heart chambers (LV EDD 66.8 mm, LV ESD 54.9 mm, RVD 33.1 mm)
- Hepertrophy of LV (LVPW 15.8 mm, VST 15.6 mm) and RV (6.8 mm)
- Decreased contractility of LV, EF 36%
- Hypokinesia of posterior wall, septa, apex, and anterio-lateral well of the LV
- Apical aneurism (28 mm length)
- Diastolic dysfunction of LV 2 degree (pseudonormal)
- Regurgitation: mitral valve 2 degree
                   tricuspid valve 2 degree
                   pulmonary valve 1 degree
- Pulmonary HTN 3 degree (41.3 mm Hg)

Thyroid US

Diffuse-nodular hyperplasia of the thyroid gland

RL 60.1×20.5×23.5 mm

LL 67.8×20.54×20.6 mm

Ist 9.0 mm

Left lobe node 8.3 mmØ

Abdomen US

- **Liver** is enlarged (craniocaudal dimension17.3 cm, left lobe – 8.9 cm), echogenicity is increased, signs of steatosis 2 degree
- **Gall bladder** content is not homogeneous, stones are not evaluated
- **Pancreas** has increased echogenicity due to microfocal fibrous changes, caused by fatty infiltration
- **Spleen, Kidney Adrenal** US are unremarkable

Chest X-ray

- Signs of venous congestion of the lungs
- Initial signs of basal pneumofibrosis of both lungs
- Lung roots are structured
- Sinuses are free
- Heart borders are displayed to the left
- Aorta is enlarged

Diagnosis

Main:

Familial combined hyperlipoproteinemia (Fredrickson type 2B).

Acute coronary syndrome: Unstable angina IIB. Postinfarction (STEMI 2014, 2015) cardiosclerosis. Essential hypertension III degree III stage. Heart failure with left ventricular systolic and diastolic dysfunction, EF 36%. III functional class NYHA. Stage D AHA. Risk score 4 (very high). Type 2 diabetes mellitus, insulin dependent, severe course. Nonalcoholic fatty liver, 2 degree.

Concomitant: Nodular goiter I degree, euthyroid state

Management
Lifestyle Modification

- Avoid smoking and alcohol intake

- Lowering of body weight

- Diet: restriction of saturated fats and simple sugars, low animal fat, low sodium (less 6 g)

Treatment

- Bisoprolol 5 mg od
- Ramipril 5 mg od
- Aspirin 75 mg od
- Clopidogrel 75 mg od
- Rosuvastatin 40 mg od
- Choline Fenofibrate 135 mg
- Insulin human NPH 20 IU 2 td 8-00, 20-00
- Insulin human 10 IU 3 td before meal

Prognosis

- In this case prognosis is unfavorable
- IHD and T2DM had developed in young age, the course of disease is progressive, symptoms are poorly controlled
- Risk estimates based on risk charts and scores used in the general population, probably grossly underestimate the real risk of the FCH patient

Conclusion

For practitioners it is advised

- monitoring the therapy not only by lab tests, but also by evaluating other instrumental and clinical markers of CHD

- following the theory of "the lower, the better", treating these patients in order to reduce their cholesterolemia and triglyceridemia to the best goals suggested by the international guidelines for cardiovascular diseases prevention, in association with a rigid control of all associated risk factors

- screening family members of people with FCH is the most effective option for early detecting cases across the whole population and prevention of CVD and CAD