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Noonan's Syndrome

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What is Noonan's syndrome (NS)?



- **Noonan syndrome** is a pleiomorphic autosomal dominant disorder with cardinal features such as short stature, distinctive facial dysmorphism, webbed neck, and heart defects
- Noonan syndrome (NS) is a relatively common congenital disease that affects both males and female equally



History 1.2.

- **The first** reported patient with what is now called Noonan syndrome was reported by Kobylinski **in 1883**: the individual in question was a 20-year old male with marked webbing of the neck, which was a feature that seemed to prompt a majority of the early reports
- **In 1902**, Funke described a patient with a webbed neck, who also presented with a short stature, cubitus valgus (a deformity of the elbow), micrognathia (undersized jaw) and other minor abnormalities
- Reports of so-called “male Turner syndrome” or Turner phenotype have been abundant throughout the 1960s, but a vigorous attempt to find an underlying chromosomal abnormality was unsuccessful



History 2.2.

- In **1962**, a pediatric **cardiologist Jacqueline Noonan** presented a clinical study of associated non-cardiac malformations in children with congenital heart disease at the Midwest Society for Pediatric Research, where she also described nine patients that shared distinctive facial features and who had a short stature, pulmonary stenosis and significant chest deformities
- In 1968 she published these nine and an additional ten patients in the *American Journal of Diseases of Children*
- Pediatrician John Opitz proposed the eponym Noonan syndrome, which was adopted in recognition of dr. Noonan, as she was the first to indicate that this condition occurs in both sexes, is familial in certain cases, includes congenital heart defects and is associated with normal chromosomes
- In 1994, the gene for Noonan syndrome was mapped to the long arm of chromosome 12 and named *NS1*
- Noonan syndrome is now known to be a genetically heterogeneous disorder with practically one half of all cases caused by gain-of-function mutations in *PTPN11*, the gene encoding the SHP-2



Synonyms of NS

- Female pseudo-Turner syndrome
- Male Turner syndrome
- NS
- Turner phenotype with normal chromosomes (karyotype)



Incidence

- It is believed that between approximately 1 in 1000 and 1 in 2500 children worldwide are born with NS
- It is one of the most genetic syndromes associated with congenital heart disease, similar in frequency to DOWN SYNDROME
- However, the range and severity of features can vary greatly in patients with NS
- Therefore, the syndrome is not always identified at an early age

Autosomal dominant

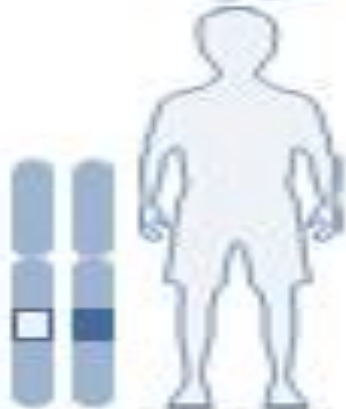
Affected father



Unaffected mother



■ Unaffected
■ Affected



Affected son

Unaffected daughter

Unaffected son

Affected daughter



Causes of NS

- **NS is caused by a genetic mutation and is acquired when a child inherits a copy of an affected gene from a parent**
- **Types** - based on the gene in which mutation has occurred, NS is of 5 types:
 1. NS1 – PTPN11 (50%)
 2. NS2 – Unknown (autosomal recessive)
 3. NS3 – KRAS (less than 5%)
 4. NS4 – SOS1 (13%)
 5. NS5 – RAF1 (3-17%)



Characteristics of NS

The 3 most common features :

1. Unusual facial features
2. Short stature (restricted growth)
3. Heart defects present at birth (congenital heart disease)

Unusual features :

1. A broad forehead
2. Drooping eyelids (ptosis)
3. A wider-than-usual distance between the eyes
4. A short, broad nose
5. Low-set ears that are rotated towards the back of the head
6. A small jaw
7. A short neck with excess skin folds
8. A lower-than-usual hairline at the back of the head and neck

CLINICAL FEATURES

- Broad forehead
- Coarse hair
- Flat nasal bridge
- Occular hypertelorism
- Small receding chin
- Sad facial expression
- High arched palate
- Dental anomalies with malocclusion\cleft uvula
- Mental retardation
- Webbing of neck
- Congenital heart disease



Clinical features

Inverted triangle-shaped head

Coarse facial features

Curly/wooly hair

Wide forehead

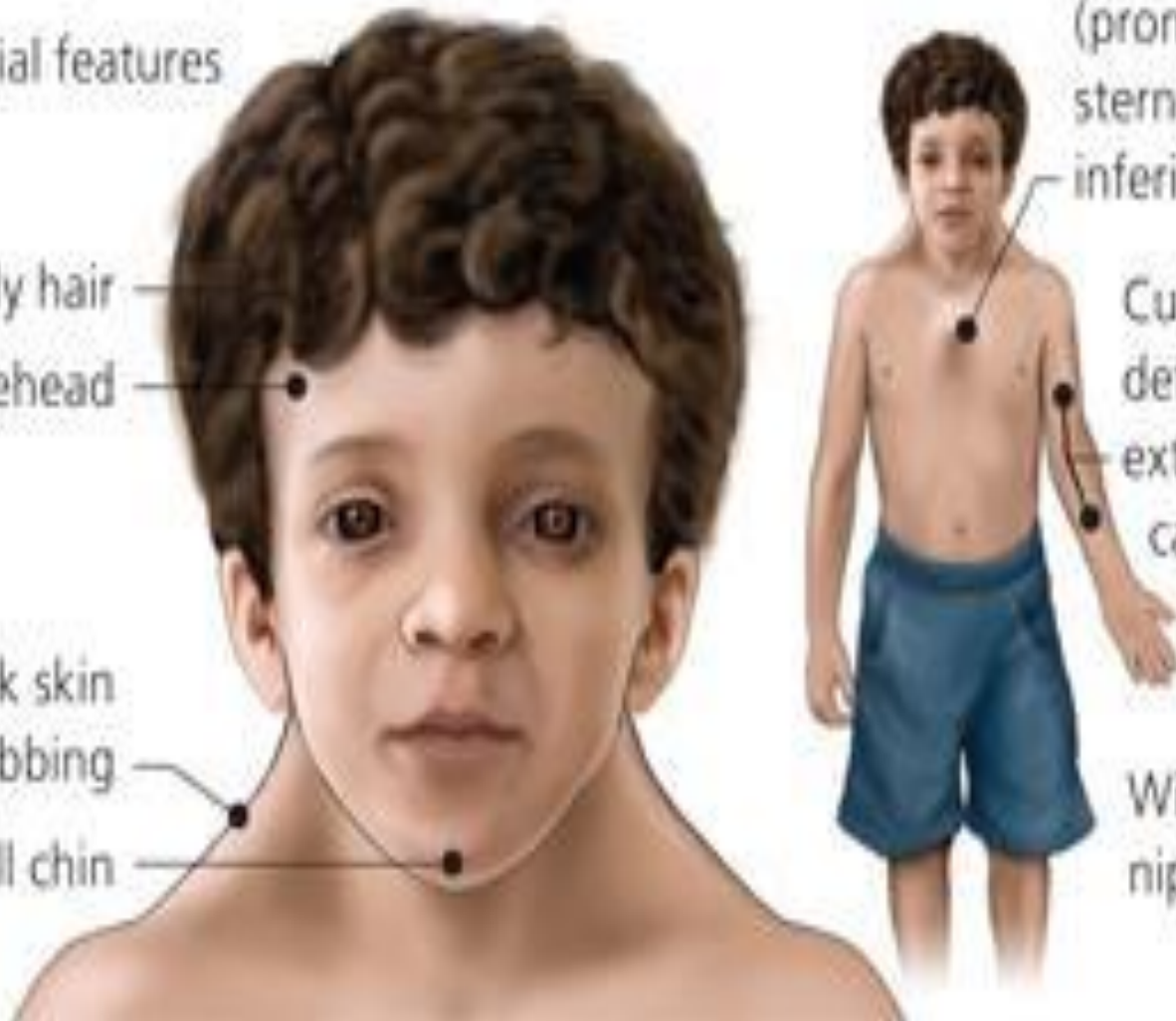
Neck skin webbing

Small chin

Pectus sternal deformity
(prominent superior
sternum and depressed
inferior sternum)

Cubitus valgus
deformity of upper
extremity (increased
carrying angle at
elbow joint)

Widely spaced
nipples





Differential diagnoses

- Costello syndrome
- Craniofaciocutaneous syndrome
- Fetal hydantoin syndrome
- Lentigines, electrocardiographic (conduction abnormalities), ocular (hypertelorism), pulmonary (stenosis), abnormal (genitalia), retardation (of growth), and deafness (LEOPARD) syndrome
- XO/XY mosaicism
- Turner syndrome
- Neurofibromatosis type 1
- *SPRED1* spectrum



Complications of the NS

- Developmental issues
- Bleeding and bruising
- Complications from lymphatic conditions
- Genital and urinary tract complications



Our patient profile

- 23 years old (05.10.1993)
- Male
- Works as an engineer
- Lives in a town
- Hospitalized for a planned course of treatment on 29.02.16



Complaints

- Dyspnea (observed during physical exertion (climb to the 7th floor) and relieved at rest)
- Dizziness (sometimes!) – when he changes his body position from horizontal to vertical (orthostasis)
- General fatigue



Medical history

- Congenital heart disease was diagnosed in the hospital at birth
- In 2002 an endovascular dilation of valvular stenosis of the pulmonary artery was made
- He is being under a heart surgeon supervision at the Institute of MHS Amosov with diagnosis : Condition after endovascular dilation of valvular stenosis of the pulmonary artery
- Residual pulmonary stenosis, secondary atrial septal defect
- Last consultation on 03.07.13 he was recommended to undergo a conductive plastic surgery by an occluder for the atrial septal defect



History of life

- Was born in a full family
- In 2001 he underwent tonsillectomy
- Denies tuberculosis, malaria, viral hepatitis, sexually transmitted diseases and AIDS
- Denies allergic reactions to drugs
- Denies smoking
- Denies alcohol consumption
- Hereditary (Father – essential hypertension, IHD, MI)



Objective state 1.6.

- The general condition is satisfactory, consciousness is clear, emotionally stable, optimistic mood
- Height = 168 cm, Weight = 70 kg
- Skin is normal
- Peripheral lymph nodes are not palpable
- The thyroid is not palpable



Objective state 2.6.

- **Respiratory system :**

- Pulmonary percussion-resonant sound
- Pulmonary auscultation-vesicular breathing (no adventitious sounds)

- **Cardiovascular system :**

- Apex in 5th intercostal space (normal) evidence of RV and RA enlargement
- HR=48 bpm
- Auscultation of the heart-continues diffuse parasternal systolic murmur, pulmonary valve diastolic murmur, tricuspid valve systolic murmur, mitral valve mild systolic murmur, aortic valve-normal sounds (no evidence of murmur)
- BP sin=112/74 mmHg, BP dextr=110/72 mmHg



Objective state 3.6.

- **Gastrointestinal system :**
 - Abdomen is soft, painless, symmetrical
 - No visible peristalsis
 - Liver is not palpated
 - Spleen and pancreas are not palpated

Objective state 4.6.



- Triangular face shaped
- Webbed neck
- Small chin
- Thick helix
- Incomplete folding ears
- Low set and widely spaced nipples
- Mild signs of gynecomastia

Objective state 5.6.



- Webbed neck
- Low posterior hairline

Objective state 6.6.



- Ocular hypertelorism
- Drooping of the upper eyelids (ptosis)
- "Hooded" eyelids



Examination

- Examinations in the hospital:
 1. Complete blood test
 2. General urine test
 3. ECG
 4. EchoCG
 5. Biochemical blood tests
- Additional instrumental methods :
 1. Ultrasonography of the abdomen (liver, gallbladder, pancreas, kidney)
 2. Holter monitoring
- Our additional recommended examinations:
 1. Genetic counselling
 2. Fertility issues
 3. Neuropsychological and behavioral issues
 4. Coagulation screening
 5. Thyroid screening
 6. Dental screening
 7. Vision screening

Complete blood test (01.03.16) 1.2.

MEASURE	RESULT	RATE
RBC	5,37	4,00 – 5,00 ($10^{12}/L$)
Hemoglobin	167	130 – 160 (g/l)
HCT	48,2	40,0 – 48,0 %
MCV	89,8	80,0 – 100,0 (fL)
MCH	31,1	28,0 – 36,0 (pg)
MCHC	346	310 – 370 (g/l)
RDW-CV	13,6	10,0 – 16,5 (%CV)
PLT	303	180 – 320 [$10^9/L$]
PCT	0.17	0.10 – 1.00 (%)
MPV	5.7	5.0 – 10.0 [fL]
PDW	17.3	12.0 – 18.0 [%]
ESR	2	M 2-12 mm/h

Complete blood test (01.03.16)

2.2.

MEASURE	RESULT	RATE
WBC	7,0	4,0 - 9,0 ($10^9/L$)
Neutrophils	63,8	47-72 %
Lymphocytes	27,7	19-37%
Monocytes	4,6	3-11 %
Eosinophils	2,9	0,5-5,0%
Basophils	1	1-1,0 %

Conclusion : slight elevation in RBCs , HGB ,HCT values may be due to compensatory mechanism in response to decrease in O₂ saturation due to PH



General urine test (01.03.16)

MEASURE	RESULT	NORMAL RANGE
SPECIFIC GRAVITY	1,026	1,001-1,040
REACTION	5,5	5,0-7,0
PROTEIN	absent	to 0.033 g / l
GLUCOSE	absent	Absent
LEUCOCYTES	2-3	6-8
EPITHELIUM TRANSITION	Not detected	Not detected
BACTERIA	Not detected	Not detected

Conclusion: normal

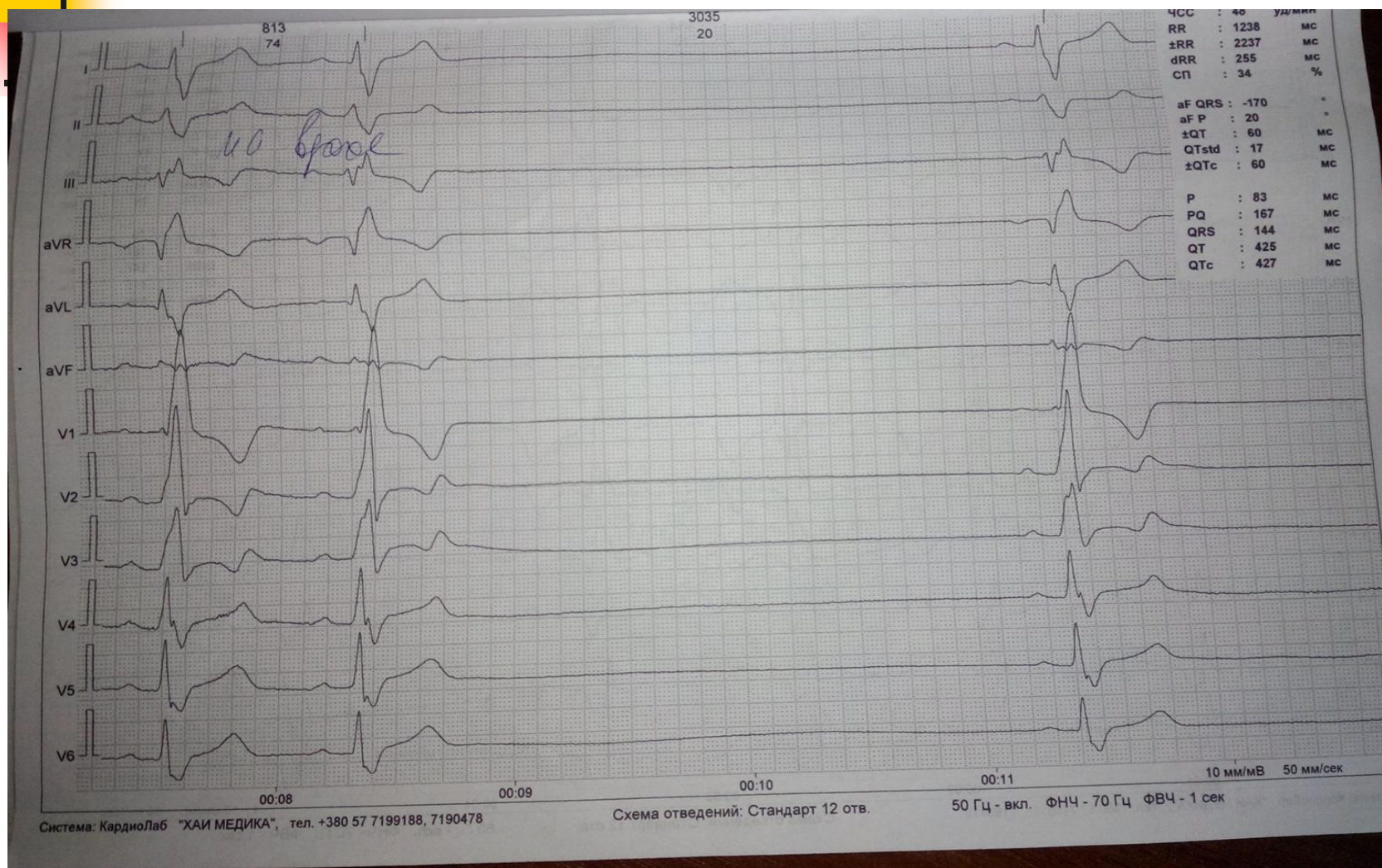


Biochemical blood test (01.03.16)

MEASURE	RESULT	NORMAL RANGE
AsAt	16	<37 u/L
AlAt	18	<41 u/L
Total bilirubin	10.18	8,6-25,5 mcmol/L
Fasting glucose	5.57	4,2-6,1 mmol/l
Creatinine	72	80-115 mcmol/L

Conclusion: normal

ECG (01.03.16) 1.4.

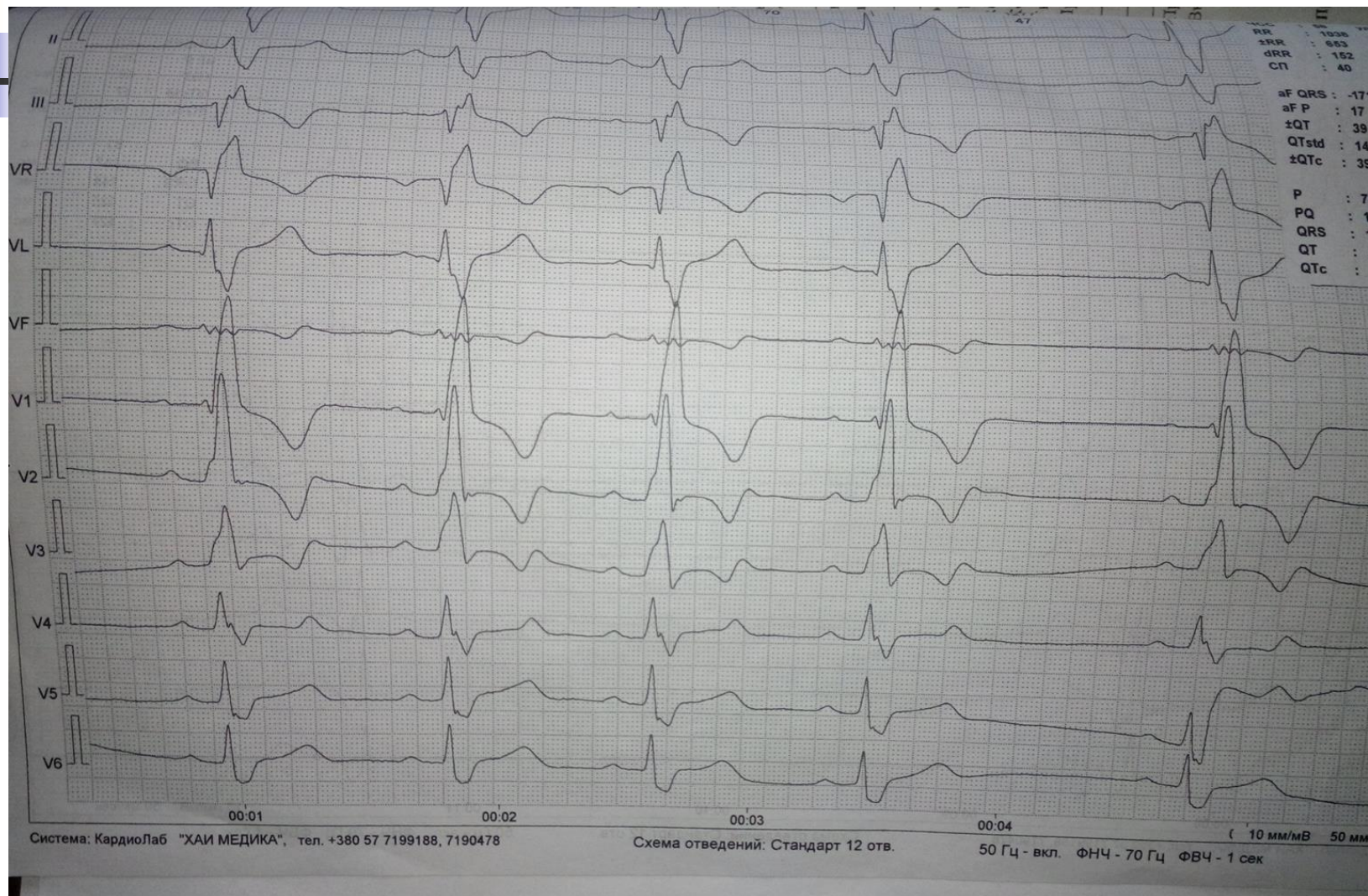




Conclusion of the ECG 2.4.

- Sinus rhythm, irregular
- Sinus arrest during inhale (pause 3035 ms) - asymptomatic
- RBBB morphology
- Right ventricular hypertrophy with strain
- Heart rate (HR)-47 beats per min (bpm)

ECG (01.03.16) 3.4.





Conclusion of the ECG 4.4.

- Sinus (respiratory) arrhythmia
- RBBB morphology
- Right ventricular hypertrophy with strain
- HR- 58 bpm

Echocardiography (01.03.16)

1.4.

NAME	RESULT	NORMAL
Acoustic window	middling	good
Aorta	29,6	20-37 mm
Aortic valve	19,3	17-26 mm
Left atrium	33,6	<38 mm
EDV of LV	46,2	35-55 mm
ESV of LV	31,5	23-38 mm
Mitral valve	Physiological regurgitation 1 degree	
Posterior wall of LV	10,6	6-11 mm
Interventricular septum	11,6	6-11 mm
Right ventricle	31,6	9-26 mm



Echocardiography 2.4.

NAME	RESULT	NORMAL
Right atrium	45,2	<44 mm
Tricuspid valve	Physiological regurgitation I-II degree	
Pulmonary valve	Cusps abnormal changed Regurgitation I-II degree The amplitude of the wave "a" -2 mm Vmax=282.4 sm/sec P gradient=31,6 mm Hg MPAP=21,7 mm Hg	The amplitude of the wave "a" = 4-10 mm
Ejection fraction	60	55-78%



Echocardiography 3.4.

NAME	RESULT	NORMAL
Interatrial septum	Violation of the integrity of the atrial septum in the middle part of the projection - defect IAS up to 8.3 mm and abnormal reflux from the left atrial cavity to the right with Gpeak about 4,8 mm Hg	



Conclusion of EchoCG 4.4.

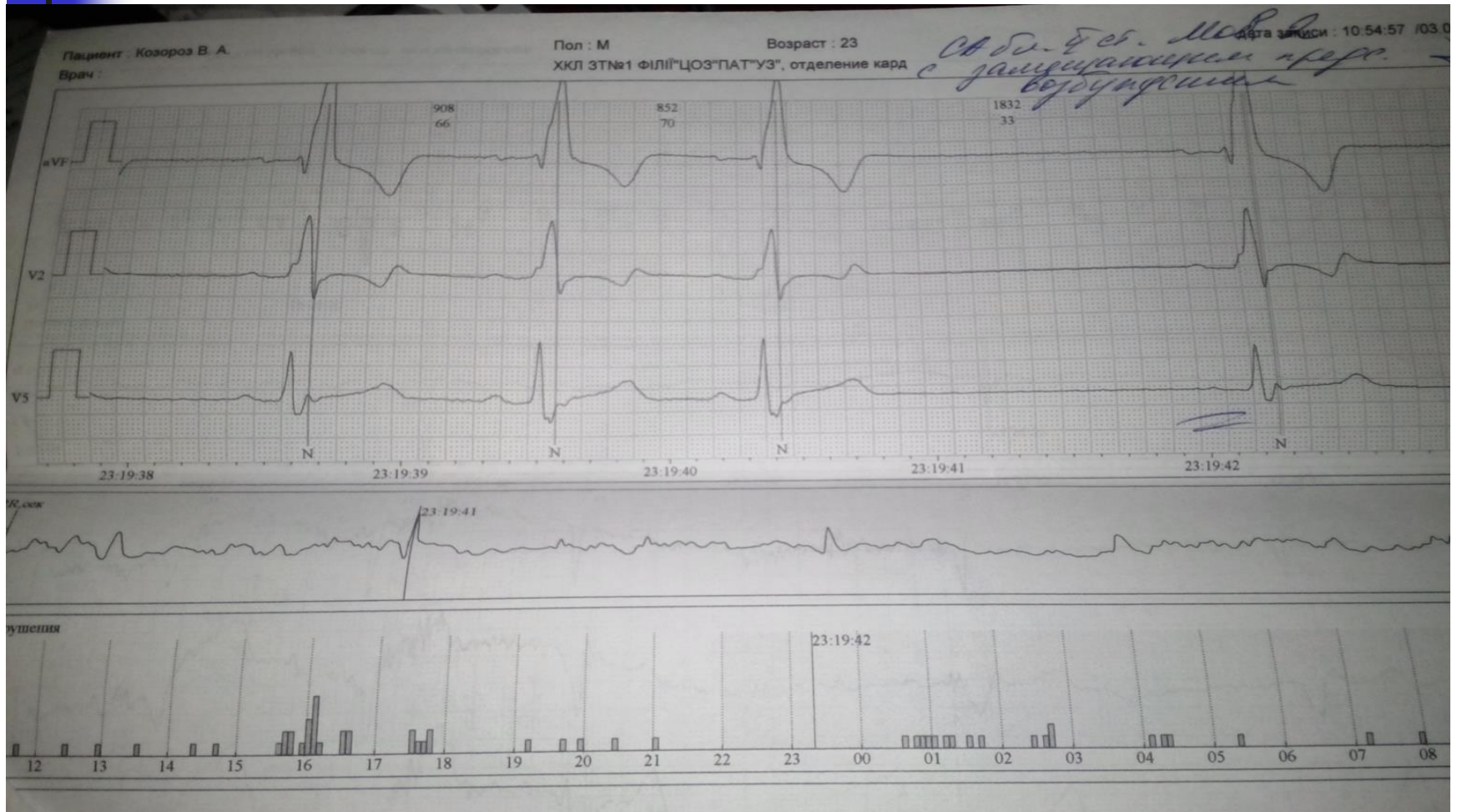
- Signs of pulmonary valve stenosis 1nd degree
- RV hypertrophy
- Dilation of the RV and RA
- Mitral regurgitation 1st degree
- Tricuspid and pulmonary valve regurgitation 1st and 2nd degree
- Pulmonary hypertension 1st stage
- Defect of the central part of atrial septum with left to right shunt
- Additional chord in the left ventricular lumen, not hemodynamically significant

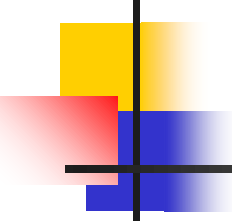


Holter monitoring (03.03.16) 1.2.

Conclusion :

- Against the background of sinus rhythm with RBBB average daily HR - 74 beats / min and mean nocturnal HR - 54 bpm, recorded maximum HR- 181 bpm (patient " ran up the stairs ") and minimal HR - 38 bpm at 05:22:05
- Circadian index 1,37 (N 1,24-1,44)
- During the entire period of monitoring were recorded frequent sinoatrial blockades II degree Mobitz 1 and Mobitz 2 with a maximum pause -1832 ms at 23:19
- Also a single ventricular premature beats were recorded (total 2)





Ultrasonography of the abdomen (01.03.16)

■ **Conclusion :**

1. kidney salt diathesis
2. Right nephroptosis



Consultation of heart surgeon- arrhythmologist (10.09.16)

Conclusion:

- ☐ According to Holter ECG with solitary episodes of SA blockades and solitary asymptomatic episode of sinus arrest (01.03.16) are not clinically significant
- ☐ There are no indications for pacemaker implantation



Basic clinical syndromes

- ☐ Congenital heart defects
- ☐ Pulmonary hypertension
- ☐ Erythrocytosis, hemoconcentration
- ☐ Arrhythmias (persistent SA blockade)
- ☐ Heart failure
- ☐ Multiple stigmas of disembryogenesis



THE CLINICAL DIAGNOSIS ACCORDING TO CURRENT CLASSIFICATIONS

Diagnostic features of NS (Van Der Burgt 1997)

Feature	A=MAJOR	B=MINOR
1.Facial	Typical face (facial features of NS vary over time)	Suggestive face
2.Cardiac	Pulmonary valve stenosis and/or hypertrophic cardiomyopathy	Other cardiac defect
3.Height	< 3 rd centile	< 10 th centile
4.Chest wall	Pectus carinatum/excavatum	Broad thorax
5.Family history	1 st degree relative with definite NS	1 st degree relative suggestive of NS
6.Other	Mild developmental delay, cryptorchidism and lymphatic dysplasia	Mild developmental delay, cryptorchidism and lymphatic dysplasia



Definitive NS

Criterion 1A+	Criterion 1B+
<ul style="list-style-type: none">One of 2A-6ATwo of 2B-6B	<ul style="list-style-type: none">Two of 2A-6AThree of 2B-6B



Sinoatrial (SA) block

Classification

- ★ In 1st-degree SA block, the SA node impulse is merely slowed, and ECG is normal
- ★ Second degree sinoatrial block is categorized into type I and type II
 - ★ 2nd-degree type I SA block (Wenckebach) demonstrates progressive shortening of the R-R or P-P intervals until a P wave is blocked in the SA node (which would not appear on the ECG)
 - ★ 2nd-degree type II SA block occurs when there are consistent R-R and P-P intervals, then a P wave is blocked in the SA node (not seen on the ECG); the subsequent "sinus pause" is an exact interval of the preceding R-R intervals (usually two times)
- ★ In 3rd-degree SA block, conduction is blocked; P waves are absent, giving the appearance of sinus arrest

Functional classification of pulmonary hypertension modified after the NYHA functional classification according to the WHO 1998

Class	Objective Assessment
I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope
IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity



Clinical classification of pulmonary arterial hypertension associated with congenital heart disease

1. Eisenmenger's syndrome

Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present

2. PAH associated with prevalent systemic-to-pulmonary shunts

- Correctable
- Non-correctable

Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.

3. PAH with small/coincidental defects (b)

Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echo), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contra-indicated.

4. PAH after defect correction

Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative haemodynamic lesions.

PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance.

a With surgery or intravascular percutaneous procedure.

b The size applies to adult patients. However, also in adults the simple diameter may be not sufficient for defining the haemodynamic relevance of the defect and also the pressure gradient, the shunt size and direction, and the pulmonary to systemic flows ratio should be considered

Echocardiographic and Doppler parameters used in grading pulmonary regurgitation severity

Parameter	Mild	Moderate	Severe
Pulmonic valve	Normal	Normal or abnormal	Abnormal
RV size	Normal	Normal or dilated	Dilated
Jet size by color Doppler [§]	Thin (usually < 10 mm in length) with a narrow origin	Intermediate	Usually large, with a wide origin; May be brief in duration
Jet density and deceleration rate – CW [†]	Soft; Slow deceleration	Dense; variable deceleration	Dense; steep deceleration, early termination of diastolic flow
Pulmonic systolic flow compared to systemic flow –PW [¶]	Slightly increased	Intermediate	Greatly increased

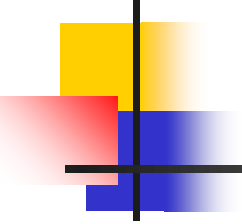
THE NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION (FUNCTIONAL CAPACITY) OF CHF

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

AMERICAN HEART ASSOCIATION HEART FAILURE STAGES

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Classification of the severity of pulmonary stenosis



	Mild	Moderate	Severe
Peak velocity (ms)	<3	3-4	>4
Peak gradient (mm Hg)	<36	36-64	>64

Recommendations for the management of Noonan Syndrome

~ in adulthood (1) ~

AGE 18+

Recommended Testing/Screening		Clinical Management Recommendations	
• Genetic counselling		Refer for genetic counselling, mutation testing and discussion of risks to children and options in pregnancy.	
• Fertility issues		Care providers should be made aware of the increased risk of infertility in males with NS, and not just in those with cryptorchidism.	
	ABNL	Refer to a fertility clinic or endocrinologist if necessary.	
• In pregnancy		Prenatal features include; polyhydramnios, increased nuchal translucency, hydrops fetalis and cystic hygroma, with or without associated ascites, pleural effusion, renal abnormalities and congenital heart defects.	
	Fetal considerations	Chorionic villus sampling (CVS) or amniocentesis is possible—referral to a clinical genetics service preconceptually is ideal— if parental mutation is known and couple wish for a prenatal diagnosis.	
		Ultrasounds at 12—14 and 20 weeks and undertake mutation analysis if parental mutation known and clinical features are suggestive, if required.	
	Maternal considerations	Potential difficulties, for example those arising from coagulation defects during childbirth, should be considered and planned for as appropriate.	
• Neuropsychological and Behavioural Issues		Repeat neuropsychological assessment if patient is symptomatic of mood/anxiety disorder(s), or if cognitive impairments are suspected.	
		Pay extra attention to the evaluation of social cognition and social embedding.	
	ABNL	Consider the risk of under-diagnosing because of problems in expressing emotions. If necessary, consider pharmacological management.	
		Facilitate access to support for employment, self help and independent living.	
		Social skills intervention as needed.	
• Neurology—potential complications in NS include seizures, craniosynostosis, hydrocephalus and Arnold Chiari malformation)		Low threshold for investigation of neurological symptoms e.g. consider Arnold-Chiari malformation and hydrocephalus if patient presents with headache or other neurological symptoms, and refer for MRI if suspected.	
	ABNL	Management of specific complications, including epilepsy, will be as per the general population.	
• Coagulation screening		Screen before any surgical intervention, and withhold aspirin prior to surgery, as per standard practice.	
• Cardiac screening		Newly diagnosed adults: full cardiac evaluation including ECHO.	
		Previously diagnosed adults: regular cardiac assessment of existing heart disease, or cardiac evaluation incase aortic disease missed previously.	
	Pulmonary artery intervention	Follow up for pulmonary valve insufficiency.	

Recommendations for the management of Noonan Syndrome

~ in adulthood (2) ~

AGE 18+

Recommended Testing/Screening	Clinical Management Recommendations
• Thyroid screening	Screen blood for thyroid abnormalities every 3—5 years.
• Lymphoedema	ABNL Manage anomalies as in general population.
• Skin problems: Keratosis Pilaris/Ulerythema	ABNL There is an increased risk of developing lymphoedema in NS, throughout adulthood. Management should be the same as for general population.
• Vision screening: squint, posterior segment ocular changes and anterior segment ocular abnormalities have been described in NS.	ABNL Avoid skin dryness, which can be worsened by long hot baths, perfumed soaps and dry atmospheres.
• Dental screening	ABNL Manage using emollients, keratolytic agents e.g. salicylic acid in urea cream, if tolerated, or short courses of topical steroids if necessary (especially if erythematous).
	Within a specialist dermatology setting, it should be noted that retinoids may not be a first choice treatment as they have been shown not to work in some NS patients.
	Unless already under ophthalmic management, NS patients should be referred to an ophthalmologist for assessment if/as appropriate.
	Published evidence on the management of routine dental problems in NS is limited.
	Routine follow up and regular dental examinations by a family dentist or local community dental services are essential.
	ABNL Missing teeth/malocclusion/other dental anomalies: refer to a consultant in dentistry for multidisciplinary management.
Giant cell lesions of the jaw	ABNL Refer to Oral/Maxillofacial/Head & Neck Surgeon or expert dental care centre.
† Anaesthesia NS can cause coagulation difficulties that should be evaluated prior to surgical procedures so that care, including anaesthesia, can be planned accordingly. Patients with NS and haemodynamically significant cardiac involvement such as severe hypertrophic cardiomyopathy need to be treated according to the usual principles for patients with such cardiovascular risk factors. Patients with NS may have craniofacial and/or vertebral anomalies that could affect intubation or the administration of spinal anaesthesia.	

14

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Complete diagnosis

■ Health facility diagnosis :

- CHD : condition after endovascular dilatation pulmonary valve stenosis (2002)
- Residual pulmonary valve stenosis
- Pulmonary valve insufficiency
- Secondary atrial septal defect
- Transient sinoatrial block II degree
- HF II A stage, II FC

■ Our clinical diagnosis :

Main:

- Noonan's syndrome

- (- CHD : condition after endovascular dilatation pulmonary valve stenosis (2002)
- Residual pulmonary valve stenosis I degree (mild severity)
- Pulmonary valve insufficiency II degree (moderate severity)
- Secondary atrial septal defect with left to right shunt
- Transient sinoatrial block II degree type I)

Complication:

- Pulmonary hypertension I class
- Right heart failure I FC, stage B



Treatment at the hospital

- Meldonium - 5,0 IV
- Trimetazidine- 35 mg twice a day



Treatment 1.3.

Lifestyle modification

Diet

- Eat vegetables and fruits and limit juice intake
- Use vegetable oils and soft margarines low in saturated fat and trans fatty acid instead of butter or most animal fats
- Eat whole-grain rather than refined-grain bread and cereals
- Reduce intake of sugar-sweetened beverages and foods
- Use nonfat or low-fat (one percent) milk
- Increase fish consumption, use only lean cuts of meat and reduced-fat meat products, and remove the skin from poultry
- **Reduce salt intake**
- Teach about a balanced meal, portion size and caloric contents of snacks
- Limit eating out and encourage eating at home



Treatment 2.3.

Lifestyle modification

- Patient require sensible advice about general activities of daily living and need to adapt to the uncertainty associated with a serious chronic life-threatening disease
- Immunization of PAH patients against influenza and pneumococcal infection is recommended
- Psychosocial support is recommended in PAH patients
- Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy
- In elective surgery, epidural rather than general anaesthesia should be preferred whenever possible
- Excessive physical activity that leads to distressing symptoms is not recommended in PAH patients



Treatment 2.3.

- The treatment of Noonan syndrome is directed toward the specific symptoms that are apparent in each individual
- Treatment may require the coordinated efforts of a team of specialists (pediatricians, cardiologists, hematologists, endocrinologists and/or other health care professionals may need to systematically and comprehensively plan an affected child's treatment)

Table 19 Recommendations for efficacy of drug monotherapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. The sequence is by pharmacological group, by rating and by alphabetical order

Drug		Class ^a -Level ^b						Ref. ^c
		WHO-FC II		WHO-FC III		WHO-FC IV		
Calcium channel blockers		I	C ^d	I	C ^d	-	-	84,85
Endothelin receptor antagonists	Ambrisentan	I	A	I	A	IIb	C	194
	Bosentan	I	A	I	A	IIb	C	196–200
	Macitentan ^e	I	B	I	B	IIb	C	201
Phosphodiesterase type 5 inhibitors	Sildenafil	I	A	I	A	IIb	C	205–208
	Tadalafil	I	B	I	B	IIb	C	211
	Vardenafil ^g	IIb	B	IIb	B	IIb	C	212
Guanylate cyclase stimulators	Riociguat	I	B	I	B	IIb	C	214

Recommendations for supportive therapy of PAH 1.2.

Recommendations	Class ^a	Level ^b	Ref. ^c
Diuretic treatment is recommended in PAH patients with signs of RV failure and fluid retention	I	C	178
Continuous long-term O ₂ therapy is recommended in PAH patients when arterial blood O ₂ pressure is consistently <8 kPa (60 mmHg) ^d	I	C	179
Oral anticoagulant treatment may be considered in patients with IPAH, HPAH and PAH due to use of anorexigens	IIb	C	84,171, 175–177

Recommendations for supportive therapy of PAH 2.2.

Correction of anaemia and/or iron status may be considered in PAH patients	IIb	C	184
The use of angiotensin-converting enzyme inhibitors, angiotensin-2 receptor antagonists, beta-blockers and ivabradine <u>is not recommended</u> in patients with PAH unless required by co-morbidities (i.e. high blood pressure, coronary artery disease or left heart failure)	III	C	



Recommended treatment

- Sildenafil 25 mg in the morning for treatment pulmonary hypertension and preventing progression of it
- Perindopril 1-2 mg in the evening to prevent myocardial remodeling
- Regular cardiac screening
- Planned conductive plastic surgery by an occluder for the atrial septal defect to prevent RV failure and as a result fluid retention



Recommendations for further examination

- ❖ Genetic counselling
- ❖ Fertility issues
- ❖ Neuropsychological and behavioral issues
- ❖ Coagulation screening
- ❖ Thyroid screening
- ❖ Dental screening
- ❖ Vision screening

Recommendations for pulmonary hypertension screening

Web Table X Recommendations for pulmonary arterial hypertension screening

Recommendations	Class ^a	Level ^b	Ref ^c
Resting echocardiography is recommended as a screening test in asymptomatic patients with systemic sclerosis.	I	B	66,76
Resting echocardiography is recommended as a screening test in <i>BMPR2</i> mutation carriers or first-degree relatives of patients with HPAH and in patients with PoPH referred for liver transplantation.	I	C	69,89,
A combined approach (including biomarkers, PFTs and echocardiography) should be considered to predict PH in systemic sclerosis.	IIa	B	66,67
Systemic sclerosis patients with a mean PAP ranging from 21 to 24 mmHg should be closely monitored, because of a higher risk of PAH.	IIa	B	75
Initial screening using the stepwise DETECT algorithm may be considered in adult systemic sclerosis patients with >3 years' disease duration and a DLCO <60% predicted.	IIb	B	67
Annual screening with echocardiography, PFTs and biomarkers may be considered in patients with systemic sclerosis.	IIb	B	66,90
In individuals who test positive for PAH-causing mutations and first-degree relatives of HPAH cases may be considered to have an annual screening echocardiogram.	IIb	C	68
Exercise echocardiography is not recommended to predict PH in high risk population.	III	C	79

DLCO = diffusing capacity of the lung for carbon monoxide; HPAH = heritable PAH; PAP = pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PFTs = pulmonary function tests; PH = pulmonary hypertension; PoPH = portopulmonary hypertension.

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.



PROGNOSIS

- **Prognosis for life** - non-compliance with doctor's appointments – non-satisfactory
- **The prognosis for recovery** - an unfavorable



THANK YOU FOR ATTENTION!