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NOONAN'S SYNDROME

Zolotarova T. V.[1], Maroun B.[1], Hanan S.[1], Mehtieva F. B.[2]
[1] V. N. Karazin Kharkiv National University, Kharkiv, Ukraine
[2] Kharkiv Railway Clinical Hospital № 1 of Brence of «HC» JSC «Ukrzaliznytsia», Kharkiv, Ukraine

The clinical case an adult patient with rare genetically heterogeneous disorder combine with congenital heart diseases and multiple stigmas of disembryogenesis, currently presenting mostly with signs of pulmonary hypertension have been reviewed. Patient is presented with definitive Noonan's syndrome according scoring system of Van Der Burgt (has 2 major criteria). The data of the laboratory and instrumental diagnostic methods, clinical diagnosis, selection of the optimized treatment and modification of the habit of life are given.

KEY WORDS: noonan's syndrome, Turner phenotype, unusual external features**,** pulmonary hypertension

СИНДРОМ НУНАН

Золотарьова Т. В.[1], Мароун Б.[1], Ханан С.[1], Мехтіева Ф.Б.[2]
[1] Харківський національний університет імені В. Н. Каразіна, м. Харків, Україна
[2] ХКЛ ЗТ № 1 Філії «ЦОЗ» ПАТ «Укрзалізниця», м. Харків, Україна

Розглянуто клінічний випадок дорослого пацієнта з рідкісним генетичним захворюванням, що поєднується з вродженими вадами серця і множинними стигмами дізембріогенезу, що на даний час переважно проявляється симптомами легеневої гіпертензії. Пацієнт представлений з визначеним діагнозом синдром Нунан згідно з системою бальної оцінки Ван Дер Бургу (має 2 головні критерії). Наведено дані лабораторних та інструментальних методів дослідження, описана діагностика, постановка клінічного діагнозу, вибір оптимальної тактики лікування та модифікація способу життя.

КЛЮЧОВІ СЛОВА: синдром Нунан, фенотип Тернера, незвичайні зовнішні ознаки, легенева гіпертензія

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Золотарёва Т. В.[1], Мароун Б.[1], Ханан С.[1], Мехтиева Ф. Б.[2]
[1] Харьковский национальный университет имени В. Н. Каразина, г. Харьков, Украина
[2] ХКБ ЖДТ № 1 Филиала «ЦЗ» ПАО «Укрзализныця», г. Харьков, Украина

Рассмотрен клинический случай взрослого пациента с редким генетическим заболеванием, сочетающийся с врожденными пороками сердца и множественными стигмами дизэмбриогенеза, в настоящее время преимущественно проявляющийся симптомами легочной гипертензии. Пациент представлен с определенным диагнозом синдром Нунан согласно системе балльной оценки Ван Дер Бурга (имеется 2 главных критерия). Приведены данные лабораторных и инструментальных методов исследования, описана диагностика, постановка клинического диагноза, выбор оптимальной тактики лечения и модификация образа жизни.

КЛЮЧЕВЫЕ СЛОВА: синдром Нунан, фенотип Тернера, необычные внешние признаки, легочная гипертензия

INTRODUCTION

Noonan syndrome (NS) is a pleomorphic autosomal dominant disorder with cardinal features such as short stature, distinctive facial dysmorphia, webbed neck, and heart defects. NS is a relatively common congenital disease that affects both males and female equally [1].

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 [2].

Synonyms of NS are: female pseudo-Turner syndrome, male Turner syndrome, Turner phenotype with normal chromosomes (karyotype) [3].

It is believed that between approximately 1 in 1000 and 1 in 2500 children worldwide are born with NS [1, 4].

NS is caused by a genetic mutation and types are based on the gene in which mutation has occurred. NS divides on 5 types: NS1 – PTPN11 (50 %), NS2 – unknown (autosomal recessive), NS3 – KRAS (less than 5 %), NS4 – SOS1 (13 %), NS5 – RAF1 (3–17 %) [1].

There are 3 most common features of NS: 1) unusual facial features, 2) short stature (restricted growth), 3) heart defects present at birth (congenital heart disease). Unusual facial features include: a broad forehead, drooping eyelids (ptosis), wider-than-usual distance between the eyes, short, broad nose, low-set ears that are rotated towards the back of the head, a small jaw, a short neck with excess skin folds, lower-than-usual hairline at the back of the head and neck [3,4].

Thus, the combination of multiple unusual facial features (different stigmas of disembryogenesis) and congenital heart defects could indicate the presence of a rare genetically determined congenital disease with a high degree of probability. This article focuses on one of such cases.

CLINICAL CASE

The patient K., a man born in 1993, was admitted to the STPI «Central clinical hospital «Ukrainian railway»» cardiology department in March, 2016 with complaints of dyspnea (observed during physical exertion (climb to the 7th floor) and relieved at rest); dizziness – when he changes his body position from horizontal to vertical (orthostasis); general fatigue.

HISTORY OF DISEASE

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 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.

ANAMNESIS VITAE

He was born in a full family. Leads a healthy lifestyle, patient does not smoke or drink, getting enough nutrition, has good living conditions. Patient denies tuberculosis, malaria, viral hepatitis, sexually transmitted diseases and AIDS: also denies allergic reactions to drugs. In 2001 he underwent tonsillectomy. Hereditary: father – essential hypertension, IHD, MI.

PHYSICAL EXAMINATION

General condition is satisfactory, consciousness is clear, emotionally stable, optimistic mood. Height = 168 cm, Weight = 70 kg. Skin is normal colored, without any scars. Peripheral lymph nodes, the thyroid gland are not palpable. Musculoskeletal system present with a lot signs of unusual features: triangular face shaped, webbed neck, small chin, thick helix, incomplete folding ears, low set and widely spaced nipples, webbed neck; also another unusual facial signs – low posterior hairline, ocular hypertelorism, drooping of the upper eyelids (ptosis), «hooded» eyelids.

Auscultation over the lungs is clear, vesicular breathing. 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 mm Hg. Abdomen is normally sized, soft and painless. Liver and spleen remain impalpable. Tapping symptom is negative on both sides.

REFERRAL DIAGNOSIS

Male Turner syndrome. Congenital heart defect. Pulmonary hypertension.

RESULTS OF LABORATORY AND INSTRUMENTAL DIAGNOSIS

Complete blood count (01/03/16): slight elevation in RBCs, HGB, HCT values may be due to compensatory mechanism in response to decrease in O2 saturation due to PH.

Urinalysis (01/03/16): all figures were in normal range.

Biochemical analysis (01/03/16): all figures were in normal range.

Electrocardiography (ECG) (01/03/16): showed irregular sinus rhythm with heart rate 47 bpm, sinus arrest during inhale (pause 3035 ms) – asymptomatic, RBBB morphology, right ventricular hypertrophy with strain.

Holter ECG monitoring (24 h) (03/03/16): showed 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).

Echocardiography (01/03/16): 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 (8.3 mm) of atrial septum with left to right shunt. Additional chord in the left ventricular lumen, not hemodynamically significant.

Ultrasonography of the abdomen (01/03/16): kidney salt diathesis, right nephroptosis; other parameters were in the normal range.

Consultation of heart surgeon-arrhythmologist (10/09/16): 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.

RECOMMENDATIONS FOR FURTHER EXAMINATION

Genetic counselling (determines the type gene in which mutation has occurred and karyotype)

Fertility issues **(**General physical examination and medical history, Semen analysis, Hormone testing ets.).

Neuropsychological and behavioral issues (intelligence tests, personality tests, perceptual-motor/memory tests).

Coagulation screening (a prothrombin time, and an activated partial thromboplastin time).

Thyroid screening (TSH, T3, T4).

Dental screening to determine the presence of other abnormalities.

Vision screening (external inspection of the eye and lids, ocular motility assessment, pupil examination, red reflex examination, visual acuity testing, ophthalmoscopy) [1–4].

CLINICAL SYNDROMES

1. Congenital heart defects
2. Pulmonary hypertension
3. Erythrocytosis, hemoconcentration
4. Arrhythmias (persistent SA blockade)
5. Heart failure
6. Multiple stigmas of disembryogenesis

CLINICAL DIAGNOSIS

Main:

Noonan's syndrome (triangular face shaped, webbed neck, thick helix, widely spaced nipples, low posterior hair line, ocular hypertelorism, ptosis, erythrocytosis).

(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.

CASE MANAGEMENT

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

RECOMMENDATIONS FOR LIFESTYLE MODIFICATION

1. Reduce salt intake.
2. Reduce intake of sugar-sweetened beverages and foods.
3. Eat vegetables and fruits and limit juice intake.
4. Patient requires sensible advice about general activities of daily living and need to adapt to the uncertainty associated with a serious chronic life-threatening disease.
5. Immunization of PAH patients against influenza and pneumococcal infection is recommended.
6. Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy.

7. In elective surgery, epidural rather than general anesthesia should be preferred whenever possible.

8. Excessive physical activity that leads to distressing symptoms is not recommended in PAH patients [1–4, 5].

RECOMMENDED TREATMENT ACCORDING LAST GUIDELINES

- Sildenafil 25 mg in the morning for treatment pulmonary hypertension and preventing progression of it [5].
- Perindopril 1–2 mg in the evening to prevent myocardial remodeling [6].
- Regular cardiac screening [2].
- Planned conductive plastic surgery by an occluder for the atrial septal defect to prevent RV failure and as a result fluid retention.

PROGNOSIS

Noonan's syndrome is a genetic disorder and prognosis for recover is an unfavorable. According to the medical literature, physicians who specialize in diagnosing and treating heart abnormalities (cardiologists) should suspect the possibility of NS in any individuals who have congenital pulmonary valve stenosis, unusual facial features and certain eye abnormalities typically found even in the more mild cases (e. g., ptosis, epicanthic folds, ocular hypertelorism) [4].

REFERENCES

1. Romano A. A. Noonan syndrome: clinical features, diagnosis, and management guidelines / A. A. Romano // Pediatrics. Official journal of the American Academy of pediatrics. – 2010. – № 126. – P. 746–759.
2. Noonan Syndrome and Related Disorders: A Matter of Deregulated Ras Signaling: [monogr. hum. genet.] /ed. M. Zenker – Basel: Karger, 2009. – Vol 17. – 166 p.
3. Allanson, J.E. Management of genetic syndromes [Noonan syndrome] / J. E. Allanson. -Whey-Li, Inc., 2005. – P. 385–395.
4. Growth standards of patients with Noonan and Noonan-like syndromes with mutations in the RAS/MAPK pathway. / [Malaquias A. C., Brasil A. S., Pereira A. C., et al.] // Am. J. Med. Genet. – 2012. – Part 158 A. – 2700–2706.
5. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and of the European Respiratory Society (ERS) //Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). – 2015. – Vol. 36, Is. 1. – P. 67–119.
6. 2012 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure:The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) // Journal of Heart Failure. – 2012. – Vol. 33, Is. 14. – P. 1787–1847.