PEDIATRICS

G.S. Senatorova, M.O. Gonchar, O.L. Logvinova, M.I. Strelkova

DIGEORDGE SYNDROME

(Case)

Kharkiv National Medical University, Ukraine

Abstract: The article presents a clinical report on DiGeorge syndrome. The study involved the assessment of disease presentation, diagnosis, inpatient management and recommendations for the follow-up treatment at home.

Key Words: DiGeorge syndrome, primary immune deficiency, children, treatment.

———————————❖———————————

Patient T., a 1.5-months-old boy, was admitted to the Intensive Care Unit in a severe condition due to cardiorespiratory failure and absence of spontaneous respiration, and was intubated with an oro-tracheal tube.

Assessment of the past and disease history showed that the child was from the 4th pregnancy, 2-nd spontaneous vaginal delivery at 38 weeks of gestation. During this pregnancy his mother experienced a threatened miscarriage at 24 weeks, an acute respiratory viral infection at 26 weeks, and asymptomatic bacteriuria from the 34-th week. Ultrasonography did not reveal any abnormalities at 11-12 weeks of gestation and anything abnormal at 25-26 weeks; echoscopic examination of fetus at the 34-th week detected signs of multiple congenital malformations (congenital heart disease, dilation of the right compartment of the heart and pulmonary artery, enlargement of the cavity of septum pellucidum to 9 mm). The findings were also indicative of hypoplasia or agenesis of the corpus collosum, hypoplasia of the vermis cerebelli, varus of the right foot, hydrocele, single umbilical artery, placental hypoplasia and polyhydramnios.

• ***Corresponding Author:***
***Olga Logvinova**, MD, PhD, Associate Professor, Department of Pediatrics 1 and Neonatology, Kharkiv National Medical University, Ukraine. E-mail: ologvinova76@mail.ru*

Family history was aggravated by multifactorial diseases: the child's mother (34 years old) had chronic pyelonephritis in remission, varicose veins of the legs. His father (36 years old) was healthy. His brother (7 years old) and sister (9 years old) were healthy.

At birth the child weighed 3150 g, his height was 53 cm, head circumference — 34 cm, chest circumference — 34 cm, Apgar score: 1 min — 7 points (2-2-1-1-1), 5 min - 8 points (2-2-1-1-2).

On the second day after the birth he was referred to a surgical correction of congenital heart defect (expansion of the aortic arch, aortic coarctation, ligation of patent ductus arteriosus) at Cardiosurgery Department. Eight days after surgical intervention he was transferred to Perinatal Center, where he was rendered respiratory support due to absence of spontaneous respiration.

He was diagnosed with hypoplastic left-heart syndrome, moderate hypoplasia of the left ventricle and aortic valve, hypoplasia of the aortic arch, patent ductus arteriosus, secondary atrial septal defect. The patient was examined by a geneticist, DiGeorge syndrome was suspected.

He was treated using open resuscitation system Aveo with respiratory support, received nutrition through a feeding tube, and was administered furosemide, captopril, verospiron, antibacterial, fungicide and immunomodulatory therapy as well as feet bandaging.

The child's condition remained severe due to evident signs of cardiorespiratory failure and absence of spontaneous respiration. He was referred to further follow-up treatment in a multi-field hospital.

On admission his consciousness was clear, his skin was pale; widespread venous network, underdeveloped subcutaneous fat layer, signs of connective-tissue dysplasia (hypermobility of the joints, hyperextensibility of the skin, varusof feet), rightsided hydrocele were detected. Visible mucous membranes were pink. Body temperature was within normal range. His heart rate was 160/min, BP — 80/60 mmHg, SpO_2 — 99%,body mass -3950 g,height -54.8 cm; head circumference — 36.5 cm, chest circumference — 35.3 cm.

The patient was intubated with an oro-tracheal tube, his respiration was harsh, and wheezing was not heard. Heart tones were rhythmic. The abdomen was soft, deeply palpable in all areas. The liver was enlarged to 3 cm below the costal margin, the spleen is +2 cm below the costal margin. Bowel movements were normal.

On admission the following diagnosis was made: DiGeorge syndrome, multiple congential malformations, congenital heart defect: hypoplastic left heart, hypoplasia of the aortic arch, aortic coarctation, patent ductus arteriosus. After surgical intervention the patient had secondary atrial septal defect, cardiomegaly, aplasia of the thymus, congenital malformation of the urinary system: grade IV hydronephrosison the leftside, congenital right clubfoot, bilateral pneumonia with confluent foci. The patient was referred to laboratory and instrumental studies with consultations by the specialists of related fields.

-Blood count:

The day in the station /№	Hb	RBC	Reticuocytes, %	Plateletes	WBC	basophils	eosinophils	granulocytes	lymphocytes	monocytes
2nd/1	79	2,8	0,87	146	4,6		1	55	36	8
4th/2	93	3,2	0,87	139	6,7		2	70	17	10
9th/3	74	2,6	0,5		4,3		1	60	31	8
13th/4	125	4,1	0,9	213	8,6		1	65	25	9
17th/5	97	3,3	0,89	165	8,2	1	1	44	52	2
13th/6	111	3,7	2,0	274	5,8		1	72	23	1

Liver function tests - ALT (N 0.14) - 0.07 mkkat/l; AST (N 0.14) - 0,083mkat/l; B-lipoproteins - 34; Cholesterol - 2,49 mmol/l; thymol test - 1.0; alkaline phosphatase - 5600 U/l; total bilirubin - 9,9 mmol/l; direct - 3.3 mmol/l; indirect - 6.6 mol/l.

- Clinical urine analysis:

The day in the station /№	Quantity	Color	CLA	SG	Protein	RBC	WBC
2nd/1	10,0	Yellow	Bland	-	None	1-2	1-3
4th/2	14,0	Yellow	Bland	-	None	1-2	1-3
9th/3	10,0	Yellow	Bland	-	None	1-2	1-3
13th/4	7,0	Yellow	Bland	-	None	1-2	1-2
23th /5	50	Light yellow	Bland	1,006	None	Changed	2-4

- Sputum analysis:

The day in the station /№	Color	Cul-ture	WBC	RBC	Epith eliu m.	Other	MBT
11th/1	White	Muco-puru-lent	10-15	1-3	Squa mose 2-4	None	Abs.
15th/2 (broncho-scopy)	Light white	Puru-lent	40-50	2-4	Squa mose 1-2	Fungus a little	Abs.

-Immunogram:

The day in the station /№	6th day/1	Norm
Leukocytes 10^9/l	10,1	10,3-11
Lymphocytes,%	14	52-69
absolutenumber, 10^9/l	1,42	5,4-7,59
T-Lymphocytes(CD_3),%	63	58-67
absolutenumber, 10^9/l	0,89	1,7-3,6
BLymphocytes. (CD_{22}),%	22	19-31
absolutenumber, 10^9/л	0,31	0,5-1,5
CD_4	45	38-50
CD_8	19	18-25
CD_4/ CD_8	2,37	1,5-2,9
CD_{16}	13	8-15
IgA,g/l	0,57	0,21±0,13
IgM,g/l	0,47	0,30±0,11
IgG,g/l	9,9	4,30±1,19
% neutrophils phagocytose	53	40-90
Phagocytes,number.	1,43	1-2
HCT-test	31	8-12
Compliment CH_{50}	42	40-80

- Bacteriological inoculation from the mouth:

K. Pneumonia 10^7, P. Aeroginosa-10^3;

K. Pneumonia 10^6, P. Aeroginosa- 10^6;

K. Pneumonia 10^4, P. Aeroginosa- 10^7;

K. Pneumonia 10^5, P. Aeroginosa - 10^7.

- Chest X-ray in the first day – bilateral upper lobe pneumonia with confluent foci. On the 13-th day – negative dynamics in the form of atelectasis of the upper lobe of the right lung (the development of segmentary pneumonia is possible). On the 17th day positive dynamics in the form of recovery of pneumatization of lung fields.

- Echocardiography:

The day in the station/№	1st day/1	8th day2	14th day/3	21st day /4	25th day/
EDD	14,3	17,7	15,5	17,4	15,7
ESD	6,1	8,8	19,2		6,8
Vd	5,3	9,3	5,7		6,8
Vc	0,5	1,5	1,6		0,7
Strokevolume	4,8	7,8	4,0		6,1
EF	90	84	71	89	88
Δ D	0,58	0,50	0,37		0,56
dLA			21,0x15,0	12,0	17,9
dRV	18,6	15,0	20,5	19,9	17,9
dRA			19,0x17,0	17,1	
ΔP AV	9,4	13,4	12,4	11,5	10,0
ΔP desc.Ao	15,4	28,5	19,8	14,7	15,1
ΔPAoV	9,3	10,9	3,8		3,9
ΔP MV	6,5	6,5	3,9		4,01
ΔP TV		4,5	5,1	5,7	5,1
Mediumpressure in PA		47,0	34	31	34
dofaorta	7,5				
daorticarch	15,5				
d abdominal. Ao	5,8				
Bloodflowintheabdominalaorta	pulsatile, c V max^2 55 см/с	Pulsatile, c V max^2 58,5 см/с	pulsatile		pulsatile
Regurgitation		I grade		I grade	I grade

- Ultrasonography of kidneys and bladder: hydronephrosis of the left kidney.

- Ultrasonography: the thymus is not visualized.

- Electrocardiography (ECG) on the 2-nd day showed the signs of severe sinus tachycardia, delayed atrioventricular conduction, incomplete right bundle branchblock, hypertrophy of the right atrium and right ventricle, repolarization disturbances. The follow-up findings indicated intensified overload of the left atrium and right ventricle as well as repolarization disturbances.

- Neurosonography: asymmetry of the lateral ventricles, cranial hypertension.

-Immunological findings: thymicaplasia, impaired cellular immunocompetence, DiGeorge syndrome.The patient was referred to chest CT to exclude malformations of the bronchopulmonary system (polycystic hypoplasia) and Wilson-Mikity syndrome.

- Hematological findings: anemia, thrombocytopenia, leukopenia requiring to exclude the development of secondary aplastic anemia. Myelography is necessary if changes in blood persist.

- Neurological findings: hypoxic-ischemic disorder of the central nervous system (of perinatal somatogenic origin), asthenic syndrome.

The patient was treated using open resuscitation system Aveo with respiratory support. He received nutrition through a feeding tube and was administered furosemide, diazepam, armadin, prednisolone, as well as antibacterial and antifungal therapy. Inhalation therapy involved pulmicort, ventolin, lasolvan; per oral thrapy - pyobacteriophagum, sildenafil, captopril, hydrochlorothiazide, verospiron, BioGaia, Laferobionum, Tobrex, caffeine-sodium benzoate (when transferring from respiratory support), pancreatine. The feet were bandaged to correct congenital clubfoot.

From the 7th day of hospital stay the patient developed low-grade fever (37.3-37.5°C), and from the 10th daypyretic fever (38.3-38.5°C) with occasional attacks of bronchospasm. He was diagnosed with secondary bilateral pneumonia with confluent foci andtype IIrespiratory failure. On the 13th day of hospital stay he was found to have negative course of pneumonic process (atelectasis of the upper lobe of the right lung and progression of segmental pneumonia). Positive course was reached by the 15th day.

By day 22, the child restored spontaneous breathing, by the 24th day he was transferred to natural feeding (mother's breast on demand).

Final diagnosis:

Multiple congenital malformations: congenital heart disease (hypoplasia of the aortic arch, patent ductus arteriosus (state after correction: expansion of the aortic arch, excision of aortic coarctation, ligation of patent ductus arteriosus), secondary atrial septal defect,circulatory failure 2A). Congenital defect of the urinary system (polycys-

tic left kidney disease, hydrocele testis). DiGeorge syndrome (thymicaplasia, impaired cellular immunocompetence). Secondary chronic obstructive pyelonephritis in remission. Interstitial lung disease (fibrosis), high pulmonary hypertension, type II respiratory failure. Grade II right-sided pneumonia. Congenital right clubfoot. Tonic and kinetic disorders resulting from hypoxic-ischemic impairment of the central nervous system. Grade II hypotrophy. Anemia, thrombocytopenia.

On the 27-th day of hospital stay the patient was discharge in a stable condition withrecommendations: nutritional care according to age; Eroton 7.5 mg 3 times per day; hydrochlorothiazide 4 mg x 2 times a day; verospiron 7.5 mg x 2 times a day; Captopril 1.4 mg x 2 times a day; Pulmicort 125 μg x 2 times a day for a month and follow-up examination in the hospital.

Literary reference

Di George's syndrome is a primary immunodeficiency characterized by aplasia or hypoplasia of the thymus and parathyroid glands, congenital heart defects, facial malformations. Moreover, the disease may be accompanied by other developmental anomalies (anomalies of the skeleton, kidneys, nervous system, eye disorders).

In absent or, which occurs more often, underdeveloped thymus T-lymphocytes do not develop properly. Therefore, the immune system cannot fully perform its protective function. However, absolute Di George's syndrome with severe abnormalities of the immune system is extremely rare. Due to the variety of symptoms, these patients can be examined by physicians of different specialties [1].

Symptoms. The incidence of this condition is similar both in male and femalepatients.

The standard history includes frequent viral, fungal and bacterial infections, poorly amenable to standard therapy.

Congenital heart defects (to the extent of tetralogy of Fallot-right ventricular outflow obstruction, high ventricular septal defect, aortic dextraposition, right ventricular hypertrophy). Convulsions (due to malfunctioning of the parathyroid glands) [2]. Abnormalities of the facial bones: microcephaly (decreased size of the skull bones); hypertelorism (wide-set eyes); small, deformed, low-set ears; epicanthus (vertical folds of skin of crescent shape covering the inner canthus); cleft lip and palate; "Gothic palate" (high palate); micrognathia (underdevelopment of the jaw bones); strabismus (squint); palpebral fissure (eye shape, in which the outer corners of the eyeballs are lowered).

Abnormalities of the larynx, pharynx, trachea, inner ear, esophagus (stenosis, shortening) [3].

Abnormalities of the central nervous system: cortical atrophy (loss of many motor and sensory functions), hypoplasia (discoordination) of the cerebellum.

Abnormalities of the gastrointestinal tract: atresia of the anus, anal fistula.

Abnormalities of the eyes: coloboma (a defect of one of the components of the eyeball (iris, lens, etc.), in which some components are missing), retinal vascular anomaly (as a result, retinal dystrophy).

Maldevelopment of the kidneys: hydronephrosis, renal atrophy, reflux.

Abnormalities of the teeth: delayed eruption, enamel hypoplasia, dental caries.

Abnormalities of the skeleton: polydactyly, absence of nails, spontaneous bone fractures.

Mental retardation and motor delay [4].

Causes. DiGeorge syndrome is caused by a deletion of the 22nd chromosome. Possible risk factors for the development of deletions are maternal diabetes, alcohol consumption during pregnancy, viral diseases in the first trimester of pregnancy.

There is evidence that damaged 22nd chromosome can be inherited in an autosomal dominant manner, that is, in humans the disease is transmitted from one of the parents [5].

Diagnostics. Assessment of medical history and presentation–mental retardation (according to parents); caries; fractures; heart problems; often recurrent bacterial, viral and fungal diseases unresponsive to treatment.

Study of life history - growth and development retardation; congenital heart defects, strabismus,recurrent bacterial, viral and fungal infections.

On examination: microcephaly, hypertelorism (wide-set)eyes, small, deformed and low-set ears, epicanthus (vertical folds of crescent-shaped skin, covering the inner canthus), cleft lip and palate, "Gothic palate", micrognathia (underdevelopment of the jaw bones), strabismus (squint), palpebral fissure (eye shape, in which the outer corners of the eyeballs are lowered). Specific sounds typical for congenital malformations of the cardiovascular system on auscultation.

Immune status is presented by low T lymphocytes and low serum immunoglobulinscan be detected as well.

Common blood count - lymphopenia.

Biochemical blood assay - decrease in the level of calcium, hypocalcemia (the assay is repeated several times to determine the persistence of this condition).

Ultrasonography of the parathyroid glands and thymus reveals their absence or dystrophy.

Echocardiography of the heart identifies defects of the cardiovascular system.

Fluorescent DNA hybridization detects a deletion of the 22nd chromosome typical forDiGeorge syndrome [6].

Treatment of the Di George's syndrome. Antibiotics are prescribed inbacterial infections,antivirals in viral infections andantifungal drugs in fungal infections. Replacement therapy with intravenous immunoglobulins derived from plasma of healthy donorsin reduced level of immunoglobulins. Calcium supplementation is prescribed in order to increase its level.

Surgical treatment implies correction of congenital malformations of the cardiovascular system.

Transplantation of fetal thymus without prior surgical correction of congenital heart disease is considered to be inefficient, only carried out inabsolute Di George syndrome (in severe immunological disorders, such as severe immunodeficiency).

Complications and consequences. Severe mental retardation.

Development of autoimmune diseases (these diseases are characterized by an aggression of the immune system against its own organism: the immune system takes over its foreign cells and attacks them). Development of neoplastic disease at early age.

Lethal outcome is possible due toinfectious complications or malformations of the cardiovascular system not compatible with life, endocrine disorders (dysfunction of the parathyroid glands).

Prognosis usually depends on the severity of cardiac and endocrine defects, absolute syndrome - on immunological findings - absence of T-lymphocytes, reduced production of antibodies-immunoglobulins**.**

Prevention. Patients with partial immune disorders can be administered prophylactic antibiotic and antifungal therapy.

It is necessary to eliminate the use of alcohol during pregnancy.

Prior to pregnancy, the mother should necessarilybe administered appropriate anti-viral vaccines (e.g., measles and rubella virus).

If routine screening(ultrasound examination of the fetus and pelvic organs at the 11-13th weeks of pregnancy)is indicative of possible DiGeorge syndrome, the pregnant woman should be referred to additional tests, particularly amniocentesis (obtaining amniotic fluid) in order to analyze fetal DNA for chromosomal abnormalities (deletions of the 22nd chromosome)[7].

Conflict of interests

There is no conflict of interests.

REFERENCES

1. Kondratenko I.V., BologovA.A. Primary immunodeficiencies – Moscow.: ID MEDPRAKTIKA-Moscow,2008, pp.23. (in Russian)

2. Allergology and Immunology. National leadership - Geotar-Media, 2009. (in Russian)

3. Bassett A.S., Chow E.W.C., Husted J. et al. Clinical features of 78 adults with 22q11 deletion syndrome// Am.J.Med.Genet. — 2015 – N 138A – P. 307 – 313.

4. Simptomy I sindromy v ehndokrinologii/Pod red. YU. I. Karachenceva. — 1-e izd. — H.: OOO «S.A.M.», Har'kov, 2006. — S. 67-68. — 227 s. — (Spravochnoe posobie). — ISBN 978-966-8591-14-3.

5. Bochkov, N.P. Nasledstvennye bolezni / N.P. Bochkov, E.K. Ginter, V.P. Puzyrev. – M. : GEHOTAR Media, 2012. – 565 s.

6. DiGeorge, A.M. Congenital absence of the thymus and its immunologic consequences: concurrence with congenital hypoparathyroidism / A. M. DiGeorge // BirthDefects Original Article Series. – 2008. – Vol. 4 (1). – P. 116–21.

7. DiGeorge, A. M. Discussion on a new concept of the cellular nasis of immunology/A. M. DiGeorge // J. Pediatr. – 2015. – Vol. 67 (5) (Suppl.). – P. 907–909.

РЕЗЮМЕ

Сенаторова А.С., Гончарь М.А., Логвинова О.Л.,
Стрелкова М.И.

КЛИНИЧЕСКИЙ СЛУЧАЙ СИНДРОМА ДИ ДЖОРДЖИ

Харьковский национальный медицинский университет

В статье освещен клинический случай синдрома Ди-Джорджи. Подробно изложены особенности течения заболевания, диагностический поиск, тактика лечения на госпитальном этапе и рекомендации по дальнейшему лечению в домашних условиях.

Ключевые слова: синдром Ди-Джорджи, первичный иммунодефицит, дети, лечение.

РЕЗЮМЕ

Сенаторова Г.С., Гончарь М.О., Логвинова О.Л.,
Стрєлкова М.І.

КЛІНІЧНИЙ ВИПАДОК СИНДРОМУ ДІ ДЖОРДЖІ

Харківський національний медичний університет

В статті висвітлено клінічний випадок синдрому Ді-Джорджі. Детально викладені особливості перебігу захворювання, діагностичний пошук, тактика лікування на госпітальному етапі та рекомендації щодо подальшого лікування вдома.

Ключові слова: синдром Ді-Джорджі, первинний імунодефіцит, діти, лікування.

Received: 03-Feb. – 2016
Accepted: 27-Mar. - 2016