DOI 10.25789/YMJ.2024.87.29

UDC 616.006.326.03

L.V. Gotovtseva, I.P. Govorova, N.I. Douglas, A.L. Sukhomyasova, T.Yu. Pavlova, A.V. Zakharova, V.M. Konstantinova

PRENATAL DIAGNOSIS OF THE 22q11.2 DELETION SYNDROME

Three cases of 22q11.2 deletion syndrome based on prenatally detected fetal anomalies are presented. The possibility of targeted prenatal diagnosis based on identified anomalies is shown.

Microdeletion syndromes are genetic diseases caused by the absence of small sections of chromosomes that are not visible under a microscope (microdeletions). Deletion syndrome (DS) of chromosome 22q11.2 (22q11.2DS) is a chromosomal aberration resulting from submicroscopic deletion (destruction) of a region of 1.5 to 3 megabases (Mb) in the region of the long arm of chromosome 22, which encodes more than 35 genes [1-7]. The incidence of this syndrome ranges from 1:3000 to 1:6000. Mortality in the first year of life is about 4% and exceeds the rates for children with a similar malformation of the cardiovascular system, but without chromosomal microdeletion, aggravated by anomaly of large vessels, hypocalcemia and tracheomalacia. It should be noted that 22q11.2 syndrome was previously classified as separate clinical syndromes: Di George syndrome (DGS), Velocardiofacial syndrome (VCFS), Conotruncal anomalies face syndrome (CTAF), Cayler cardiofacial syndrome [2].

Keywords: prenatal diagnosis, 22q11.2 deletion syndrome, congenital heart disease, fetus

GOTOVTSEVA Lucia Vasilievna – PhD, Head of the Department of Antenatal Fetal Protection of the Perinatal Center SAI RS (Y) Republican Hospital No. 1 - National Center of Medicine, Associate Professor of the Department of Obstetrics and Gynecology of the Faculty of Postgraduate Training of Doctors of the Medical Institute M.K. Ammosov North-Eastern Federal University, e-mail: lutcia@list.ru, **GOVOROVA Izabella Prokopyevna** – PhD, Doctor of the Department of Ultrasound Diagnostics of the Consultative and Diagnostic Center SAI RS (Y) Republican Hospital No. 1 - National Center of Medicine, Associate Professor of the Department of Obstetrics and Gynecology of the Faculty of Postgraduate Training of Doctors of the Medical Institute M.K. Ammosov North-Eastern Federal University, e-mail: iz-govorova@mail.ru; **DOUGLAS Natalya Ivanovna** – Doctor of Medical Sciences, Head of the Department of Obstetrics and Gynecology of the Faculty of Postgraduate Training of Doctors of the Medical Institute M.K. Ammosov North-Eastern Federal University, e-mail: nduglas@yandex.ru; **SUKHOMYASOVA Aitalina Lukishna** – PhD, Head of the Department of Medical Genetics Center SAI RS (Y) Republican Hospital No. 1 - National Center of Medicine, leading researcher of the Laboratory of Molecular Medicine and Human Geneticsof the Medical Institute M.K. Ammosov North-Eastern Federal University, e-mail: aitalinas@yandex.ru; **PAVLOVA Tatyana Yurevna** – PhD, Head of the Perinatal Center SAI RS (Y) Republican Hospital No. 1 - National Center of Medicine, Associate Professor of the Department of Obstetrics and Gynecology of the Faculty of Postgraduate Training of Physicians of the Medical Institute M.K. Ammosov North-Eastern Federal University, e-mail: tatyanaupavl@mail.ru; **ZAKHAROVA Aleksandra Vyacheslavovna** – Doctor of the Department of Antenatal Fetal Protection of the Perinatal Center SAI RS (Y) Republican Hospital No. 1 - National Center of Medicine, e-mail: zahandra@mail.ru; **KONSTANTINOVA Valentina Mikhailovna** – PhD, Head of the Department of Ultrasound Diagnostics of the Consultative and Diagnostic Center of the GAU RS (Y) Republican Hospital No. 1 - National Center of Medicine, Associate Professor of the Department of Obstetrics and Gynecology of the Faculty of Postgraduate Training of Physicians of the Medical Institute M.K. Ammosov North-Eastern Federal University, e-mail: konstavm@mail.ru

Pregnant women were consulted in the antenatal fetal care department and in the Medical Genetic Center of the Perinatal Center of the State Autonomous Institution “Republican Hospital No. 1”. Expert ultrasound examinations were carried out using a VolusonE8 (GE) device.

The combined screening was carried out and calculated in the Astraia program in the biochemical laboratory of the Medical Genetics Center. The Astraya program contains an algorithm for calculating the risk of a chromosomal abnormality (CA), developed by the Fetal Medicine Foundation-FMF. BRAHMS Kryptor is used to measure biochemical markers of the 1st trimester PAPP-A and free betahCG.

Pregnant women underwent a molecular cytogenetic study of the fetus: invasive prenatal diagnostics (amniocentesis, cordocentesis) for chromosomal microarray analysis (CMA).

Chromosomal prenatal microarray analysis was carried out in the laboratory of molecular pathology “Genomed” (Moscow). Chromosomal microarray analysis (CMA, molecular cytogenetic study, molecular karyotyping) is a test to determine structural changes in DNA that result in changes in the amount of genetic material - deletions and duplications.

Chromosomal microarray analysis is the recommended first-line test by the medical genetics community for diagnosing the causes of congenital malformations, mental retardation, epilepsy and autism, as well as microdeletion and microduplication syndromes.

Targeted chromosome microarray analysis is performed on a Genoscan 3000 genetic analyzer using low-resolution microarrays.

Results and discussion. In all cases, the first ultrasound examination did not reveal any defects or markers of fetal chromosomal abnormality, and no increase in the thickness of the nuchal translucency was observed. When conducting combined screening, serum markers were within normal limits, individual risks for trisomy were low. Patients were referred for evaluation after the second screening examination with suspected congenital heart defects and multiple malformations.

Pregnant women were diagnosed with various conotruncal heart defects and thymic hypoplasia, characteristic changes accompanying 22q11.2 deletion syndrome. Hypoplasia of the thymus was detected by measuring the thymus; a transverse measurement of the thymus was performed and the thymo-thoracic ratio (TTR) was calculated. These pregnant women showed a decrease in the perimeter of the thymus and a decrease in TTO.

All three pregnant women were diagnosed with 22q11.2 deletion syndrome;

Case Presentation 1. Patient D., 27 years old, this is her first pregnancy. The first screening took place in a private clinic at 12.3 weeks: no markers of fetal

chromosomal abnormality were detected, the thickness of the nuchal translucency was 1.5 mm.

Combined prenatal screening – PAPP-A 2.726, hCG 1.678 MoM, risks for three trisomies are low. At screening in the 2nd trimester with suspected MVD, the patient was sent for examination at 20.2 weeks to the Perinatal Center. An echographic examination of the fetus revealed multiple congenital malformations of the fetus. TPS: Common truncus arteriosus. Ventricular septal defect. Anomaly of facial development: bilateral cleft lip and palate. Hypoplasia of the thymus. Amniocentesis was performed to conduct molecular cytogenetic analysis.

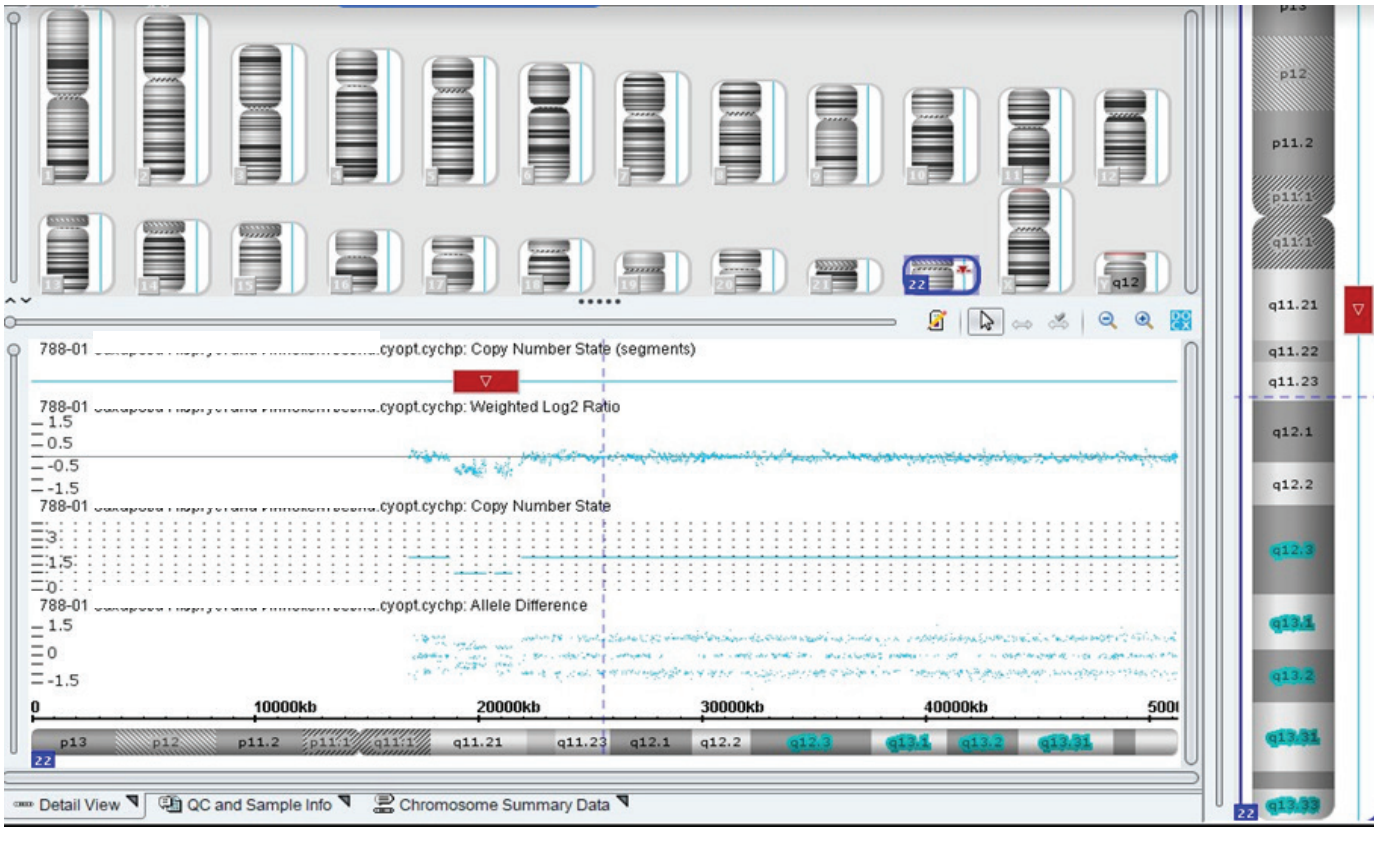
Molecular karyotype (according to ISCN 2016): arr[hg19] 22q11.21(17965842_20177061)x1. There is a microdeletion of a region of the long arm (q) of chromosome 22 from position 17965842 to position 20177061, covering the region 22q11.21. Microdeletion and microduplication syndromes associated with imbalance (OMIM): Chromosome 22q11.2 deletion syndrome (OMIM: 188400). After confirmation of the chromosomal abnormality of the fetus, the prenatal council decided to terminate the pregnancy with pathological verification of the diagnosis.

Case presentation 2. Patient Z., 31 years old. From the anamnesis - 3 marriages, 3 births from previous marriages. The first screening took place at the Central Regional Hospital at 11.6 weeks: the thickness of the nuchal translucency was 1.9 mm, no markers of fetal chromosomal abnormality were identified. Combined screening – PAPP-A 0.775, beta-hCG 0.518 MoM, individual risks for trisomy are low. After the 2nd screening ultrasound, she was sent for examination to the Perinatal Center. An echographic examination at 20.4 weeks revealed multiple congenital malformations. CHD: double origin of vessels from the right ventricle, large high ventricular septal defect. Anomaly of facial development: bilateral cleft of the upper lip and hard palate. Developmental anomaly of the musculoskeletal system: postaxial polydactyly of both hands. Bilateral ventriculomegaly. Hypoplasia of the thymus. Based on the identified changes, cordocentesis was performed for chromosomal microarray analysis. Molecular karyotype (according to ISCN 2016): arr[hg19] 22q11.21(18917030_21804886) x1. There is a microdeletion of a region of the long arm (q) of chromosome 22 from position 18917030 to position 21804886, covering the region 22q11.21. Microdeletion and microduplication imbalance-associated syndromes (OMIM): 22q11.2 deletion syndrome (OMIM: 188400, 192430).

Considering multiple defects and microdeletion syndrome, the pregnancy was terminated by decision of the prenatal consultation. The pathological examination confirmed the diagnosis.

Case Presentation 3. Patient T., 29 years old. From the anamnesis of 3 births, the third birth - early neonatal mortality, 2 medical abortions. The genealogical history is burdened by a congenital facial defect (in a nephew): cleft palate.

The first screening ultrasound examination was carried out at the Central Regional Hospital at 11.3 weeks: the thickness of the nuchal translucency was 1.4 mm. Combined screening – PAPP-A 0.904, beta-hCG 0.401 MoM, low risks for chromosomal pathology. At 26 weeks, with suspected congenital heart disease, she was sent to the Perinatal Center. An ultrasound examination at 26.1 weeks revealed a congenital heart defect: absence of pulmonary valve syndrome (APSV). Expansion of the cavity of the transparent septum. Considering the high risk of 22q11.2 deletion syndrome up to 25% with this combined pathology, amniocentesis was performed.



Microdeletion of a region of the long arm (q) of chromosome 22 from position 18917030 to position 21804886, covering the region 22q11.21

Comparative table of 3 pregnancy observations

Parameters	1 observation	2 observation	3 observation
Nationality	Sakha	Sakha	Sakha
Age	27 years	31 years	29 years
Parity	1st pregnancy	births 3	births 3, termination of pregnancy -2
The 1nd trimester			
CPS	60 mm	53 mm	48 mm
Gestational age	12.3 weeks	11.6 weeks	11.4 weeks
NTT	1.5 mm (95 percentile 2.34 mm)	1.9 mm (95 percentile 2.32 mm)	1.4 mm (95 percentile 2.30 mm)
Nasal bone	visualized	visualized	visualized
PAPPa	2,726 MoM (0,5-2,0 MoM)	0,775 MoM (0,5-2,0 MoM)	0,904 MoM (0,5-2,0 MoM)
hCG	1,678 MoM (0,5-2,0 MoM)	0,518 MoM(0,5-2,0 MoM)	0,401 MoM (0,5-2,0 MoM)
Risks for trisomy (21,18,13)	1:16243; 1:>20000; 1:>20000	1:1653; 1:>20000; 1:>20000	1:137114; 1:>20000; 1:>20000
The 2nd trimester			
Congenital heart defect	common truncus arteriosus, VSD	double outlet of vessels from the right ventricle, VSD	absent pulmonary valve syndrome
Facial abnormalities	bilateral cleft lip, palate	bilateral cleft lip, palate	not identified
Thymus	hypoplasia; transverse diameter of the thymus 8 mm (5th percentile 10 mm)	hypoplasia; transverse diameter of the thymus 6 mm (5th percentile 10 mm)	hypoplasia; transverse diameter of the thymus 11 mm (5th percentile 18 mm)
Additional changes for ultrasound	not identified	ventriculomegaly; postaxial polydactyly of both hands. Microgenia	expansion of the cavity of the septum pellucidi
Invasive diagnostics	study of genomic DNA isolated from amniotic fluid cells	study of genomic DNA isolated from fetal blood	study of genomic DNA isolated from amniotic fluid cells
Chromosomal microarray analysis	microdeletion of a region of the long arm (q) of chromosome 22 from position 17965842 to position 20177061, involving the region 22q11.21 (OMIM: 188400)	microdeletion of a region of the long arm (q) of chromosome 22 from position 18917030 to position 21804886, involving the region 22q11.21(OMIM: 188400, 192430)	microdeletion of a region of the long arm (q) of chromosome 22 from position 18917030 to position 21804886, involving the region 22q11.21. (OMIM: 188400, 192430)
Outcome	Termination of pregnancy in the 2nd trimester	Termination of pregnancy in the 2nd trimester	Delivery in the Federal Center

Molecular karyotype (according to ISCN 2016): arr[hg19] 22q11.21(18917030_21804886)x1. There is a microdeletion of a region of the long arm (q) of chromosome 22 from position 18917030 to position 21804886, covering the region 22q11.21. Microdeletion and microduplication syndromes associated with imbalance (OMIM): 22q11.2 deletion syndrome (OMIM: 188400, 192430).

After confirmation of the diagnosis, at the prenatal consultation, the pregnant woman was offered termination of pregnancy, taking into account the identified changes and the unfavorable prognosis for the life of the fetus. The pregnant woman refused to terminate the pregnancy. The birth occurred on time in the Federal Center.

Conclusion: 22q11.2 deletion syndrome is a chromosomal abnormality causing a congenital malformation, the common symptoms of which are heart defects, maxillary defect,facial dysmorphia, growth restriction and immunodeficiency [2].

22q11.2 deletion syndrome in our cases was detected in the 2nd and 3rd trimester of pregnancy. With combined screening, pregnant women were not included in the high-risk group for fetal chromosomal abnormalities.

Prenatal diagnosis for the presence of a deletion of chromosome 22 is mandatory when identifying conotruncal heart defects, in combination with thymic hypoplasia, anomalies of facial development - cleft, facial dysmorphism (chorionic villus biopsy, amniocentesis, cordocentesis).

But at this stage, in the presence of an expert ultrasound machine, corresponding to the qualifications of the ultrasound doctor, and subject to a standardized anatomical protocol, prenatal diagnosis of this microdeletion is in most cases possible during the first screening examination.

References

1. Rumyantsev AG, Maschan AA. Federalnjie i klinicheskie rekomendatsii po diagnostike I lecheniju sindroma deletsii 22 chromosomji [Federal and clinical guidelines for the diagnosis and treatment of chromosome 22 deletion syndrome. 2014; 3-7 (In Russ.).]

2. Namazova-Baranova LS, Ginter OV, Polunina TA, Davydova IV, Savostyanov KV, Pushkov AA, Zhurkova NV, Mospan TYa. Sindrom deletsii 22q11.2: symptomji, diagnostika, leshenie. Voprosji sovremennoi pediatrii [22q11.2 deletion syndrome: symptoms, diagnosis, treatment. Issues of modern pediatrics. 2016; 15(6):590–595 (In Russ.).] doi: 1010.15690/vsp.v15i6.1656.

3. Medvedev MV, Buryakova SI, Zamyatina AI. Prenatalnaja pricelnaja diagnostika syndroma Di Dgordji (sindrom deletsii 22q11.2) [Prenatal targeted diagnosis of DiGeorge syndrome (22q11.2 deletion syndrome)]. Prenatalnaja diagnostika [Prenatal Diagnosis. 2019; 18 (4): 377–382 (In Russ.).] doi: 10.21516/2413-1458-2019-18-4-377-382.

4. Kozlova YuO, Shilova NV, Yudina EV, Minzhenkova ME, Zolotukhina TV. Prenatalnaja diagnostika microdeletii 22q11.2 [Prenatal diagnosis of 22q11.2 microdeletion.] Prenatalnaja diagnostika [Prenatal Diagnosis]. 2012; 11 (4): 311–315.

5. Chaoui R, Heling KS, Zhao Y, Sinkovskaya E, Abuhamad A, Karl K. Dilated cavum septi pellucidi in fetuses with microdeletion 22q11. Prenatal Diagnosis. 2016; 36: 911–915. doi: 10.1002/pd.4911

6. Bataeva R, Bellsham-Revell H, Zidere V, Allan LD. Reliability of fetal thymus measurement in prediction of 22q11.2 deletion: a retrospective study using four-dimensional spatiotemporal image correlation volumes. Ultrasound Obstet. Gynecol. 2013; 41: 172–176.

7. Chaoui R, Kalache KD, Heling KS, Tennstedt C, Bommer C, K rner H. Absent or hypoplastic thymus on ultrasound: a marker for deletion 22q11.2 in fetal cardiac defects. Ultrasound Obstet. Gynecol. 2002; 20 (6): 546–552. doi: 10.1046/j.1469-0705.2002.00864.x

Published on September 30, 2024. Format 60x84 1/8. Physical person 17.25. Edition 100 copies.

Printed from the finished original-layout in the "SMIC" printing house.
Address of the printing house: Yakutsk, 50 No. 1, Ordzhonikidze Street