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# Clinical genetic description and analysis of the case of chromosomal mosaicism mos47,XY,+8/46,XY

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**ABSTRACT**

The article describes a clinical case of chromosomal mosaicism in a boy, 4 months and 3 weeks old. Cytogenetic analysis of peripheral blood lymphocytes of the child made it possible to establish the karyotype mos47,XY,+8/46,XY with an approximately equal ratio of normal and abnormal cells. The pathogenetic effects of the mosaic form of trisomy 8 are discussed. The authors discussed the results of examination of the patient's mother during pregnancy as part of a combined prenatal screening for congenital and hereditary diseases. The difficulty in prenatal diagnosis of chromosomal mosaicism is noted and explained by the lack of specific biochemical and ultrasound markers. However, in the late pregnancy period, ultrasound signs of impaired development of the brain, heart, and kidneys associated with a chromosomal abnormality can be detected.

**Key words:** prenatal diagnosis, trisomy 8, chromosomal mosaicism, cytogenetic analysis

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# Клинико-генетическое описание и анализ случая хромосомного мозаицизма mos47,XY,+8/46,XY

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**РЕЗЮМЕ**

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Описан клинический случай хромосомного мозаицизма у мальчика в возрасте 4 мес и 3 нед. Цитогенетический анализ лимфоцитов периферической крови ребенка позволил установить кариотип mos47,XY,+8/46,XY с приблизительно равным соотношением нормальных и аномальных клеток. Обсуждаются патогенетические эффекты мозаичной формы трисомии 8. Приводятся результаты обследования матери пациента во время беременности в рамках комбинированного пренатального скрининга врожденных и наследственных болезней. Отмечается сложность пренатальной диагностики хромосомного мозаицизма в связи с отсутствием специфических биохимических и ультразвуковых (УЗ) маркеров. Однако на поздних сроках беременности могут быть обнаружены УЗ-признаки нарушения развития головного мозга, сердца и почек, ассоциированные с хромосомной аномалией.

**Ключевые слова:** пренатальная диагностика, трисомия 8, хромосомный мозаицизм, цитогенетический анализ.

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## INTRODUCTION

Complete trisomies of autosomes in humans usually lead to early intrauterine fetal death and abortion before 7–8 weeks of gestation. Trisomies on chromosomes 13, 18, and 21 are exceptions, as they are not fatal, but are accompanied by congenital malformations. Biochemical and ultrasound markers of a these aneuploidies, as a rule, are quite clearly detected from 11–14 weeks of gestation, which allows for performing prenatal screening of genetically abnormal fetuses [1].

On the contrary, mosaic variants of trisomies are not often associated with pronounced developmental anomalies and may be unrecognized during prenatal screening. Health status of such patients at birth and in the future depends on the type of chromosome involved in the abnormality and the ratio of normal and mutant cells in the body. The clinical presentation of chromosomal mosaicism is unstable, which complicates the establishment of the cause of the pathology and the final diagnosis [2].

Trisomy on chromosome 8 in newborns is a rare event as only its mosaic variant is compatible with life and currently considered an independent syndrome (constitutional trisomy 8 mosaicism syndrome, T8MS). Single studies of sufficiently large population samples give an approximate estimated frequency of the anomaly ranging from 1 / 25000 to less than 1 / 50000 [3]. Among patients, there is a heterogeneity of clinical manifestations associated, apparently, with the proportion of mutant cells in the body and their predominant localization. To date, few newborns without serious abnormalities were identified. They had demonstrated satisfactory physical and intellectual development in the future, normal life expectancy reproductive problems in adulthood [4] and even had children [5]. On the other hand, the majority of patients have pronounced malformations that are already noticeable at birth [2, 6–10].

Characteristic symptoms of T8MS with a significant proportion of mutant cells are anomalies of the axial skeleton and limbs: a short wide neck, skull deformities, scoliosis, and camptodactyly. Deep transverse folds on the palms and feet are almost always revealed. Craniofacial dysmorphisms may include protruding forehead, hypertelorism, flattened nasal bridge, upturned nose, and ear deformities and misalignment. Internal organs are usually without lethal lesions; often there is agenesis of the corpus callosum, ventriculomegaly, heart defects of varying severity, and hydronephrosis. Disorders of psychomotor development are rather mild: delayed development of speech and motor skills and moderate mental retardation [6–8, 10].

Currently, a positive association has been established between the presence of an additional 8th chromosome in the karyotype and the likelihood of myelodysplastic syndrome [11–14]. According to some data, trisomy 8 as a somatic mutation is found in 5–7% of cases of this pathology [11, 12]. It is recommended to refer patients with an identified clone of bone marrow mu- tant cells to the oncological risk group [13]. Obviously, patients with a mosaic variant of trisomy 8, established on the basis of a cytogenetic analysis of lymphocytes, automatically fall into this cohort and should be under the supervision of an oncologist.

Registration and description of all new cases of T8MS are necessary not only to assess the frequency and spectrum of chromosomal abnormalities in the population, but also to determine the correlation between the

proportion of abnormal cells and severity of clinical symptoms in a patient. The search for prenatal pathology markers by retrospective analysis of the pregnancy course in mothers with children having mosaic variant of trisomy 8 is also relevant.

## CLINICAL CASE

A boy S., 4 months and 3 weeks old, was referred to the Medical-Genetic Consultation Department of Kemerovo Regional Clinical Hospital for examination by a geneticist. The reason for the referral was a disorder in development of the external genital organs (hypospadias). At the examination, numerous craniofacial dysmorphisms were additionally revealed, such as hydrocephalic form of the skull, sunken nasal bridge, Asian-like eyes, upturned nose, abnormal auricles, and a short neck. In addition, partial cutaneous syndactyly of the 2nd and 3rd toes of both feet was revealed.

The child was born from the 1st pregnancy. The mother was 22 years old, had been overweight since childhood, was not registered at the dispensary, her work was not associated with harmful conditions, and poor health habits were absent. Intrauterine development of S. proceeded against the background of chronic placental and isthmic-cervical insufficiency, gestational hypertension, and polyhydramnios. S.'s weight at birth was 3,780 g and the Apgar score was 7/7. The child was bottle-fed, weight at the age of 4 months is 6,700 g (slightly underweight). In the maternity hospital, the following was established: moderate asphyxia, cephalohematomas over the right and left parietal bones, glanular hypospadias, and hypoconjugational jaundice.

From the maternity hospital, the child was transferred to the neonatal pathology department due to the diagnosed heart defect. Detailed examination revealed perimembranous defect of the interventricular septum, moderate stenosis of the pulmonary artery, and minor anomalies in heart development, such as open oval window and anomalies of the chordal apparatus. According to the ultrasound examination of the brain, S. had partial agenesis of the corpus callosum, moderate deformation of the ventricular system, and hydrocephalus. Cerebral ischemia of the 2$^{nd}$ degree and excitability syndrome were established. Psychomotor reactions with slight deviations included holding the head unconfidently, not always reacting to sounds, turning over on his side, following objects with eyes, reacting to toys, or smiling. Concomitant pathologies included dacryocystitis, bilateral focal pneumonia, and chronic tubo-otitis on both sides. Sensorineural hearing loss was suspected. The bilirubin level remained high and reached up to 143.9 μmol / L due to the indirect fraction.

To exclude chromosomal pathology, the child was referred for karyotyping. Cytogenetic analysis of 100 metaphase plates from peripheral blood lymphocytes revealed two clones of cells with a normal male karyotype 46,XY and trisomy on the 8th chromosome 47,XY,+8 in almost equal proportions. Thus, we can state that S. had trisomy 8 in a mosaic form with the karyotype mos47,XY,+8[52]/46,XY[48] (Figure).

This clinical case raises the question of the possibility of prenatal diagnosis of chromosomal mosaicism of the established type. We performed a retrospective analysis of the results of ultrasound and biochemical studies of S.'s mother during pregnancy. The first examination was carried out at 13 weeks of pregnancy. Fetal heart rate – 157 beats / min, crown-rump length (CRL) value – 67.4 mm, nuchal translucency (NT) – 1.1 mm. All indicators were within normal limits. The content of the free β-subunit of hCG in the blood serum of the woman was 49.5 IU / L (1.458 MoM), PAPP-A – 0.703 IU/L (0.214 MoM). Taking into account the age of the mother, the individual risk of trisomy 21 was 1:124, the risk of trisomies 18 and 13 was 1:1902 and 1:3848, respectively.

Since the risk of common chromosomal abnormalities of fetus was calculated to be low (less than 1:100), the woman was not referred for invasive prenatal testing. Further ultrasound examination of the fetus was carried out in the II trimester of pregnancy. No developmental defects associated with chromosomal abnormalities were identified.

The difficulty in prenatal diagnosis of the mosaic form of trisomy 8 is also confirmed by the previously published data. Comparison of the results of combined screening of 28 pregnancies that ended in birth of children with T8MS demonstrated that the most common (50% of cases) reason for invasive diagnosis is the age of the woman. In 18% of cases, deviations in the biochemical parameters of the pregnant women's blood were found. Finally, 21% of fetuses had ultrasound signs of developmental disorders. At the same time, the spectrum of ultrasound indicators was quite wide, which does not allow for identification of specific prenatal markers for T8MS [2].

Surprisingly, in most of the previously described cases, immediately after the birth of a child, a complex of malformations was detected, comparable to the one found in S. Three groups of anomalies were noted: those associated with the development of the brain, heart, and kidneys [2, 4, 6, 9, 10]. Obviously, with qualified ultrasound diagnostic doctors and proper equipment of medical institutions, these T8MS markers might have been detected at least in the II or III trimester of pregnancy.

## CONCLUSION

Thus, prenatal detection of mosaicism on chromosome 8 in the framework of the current screening of pregnant women is difficult. Biochemical and ultrasound indicators of an increased risk of trisomies on chromosome 13, 18, and 21 may not reflect the health status of a fetus with T8MS. Ultrasound markers of pathology become noticeable in late gestation. Malformations the heart and kidneys are noted. At the same time, the prognosis for the life and health of newborns is relatively favorable, and the severity of developmental defects, apparently, is associated with the proportion and predominant localization of abnormal cells in the body.

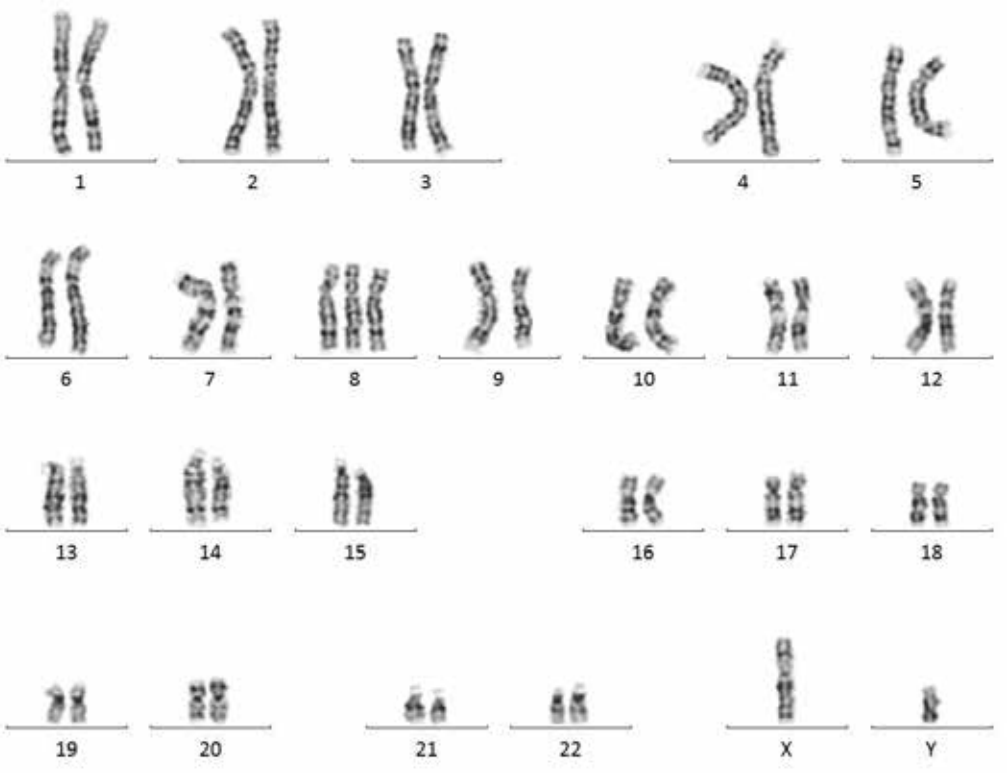


Figure. Abnormal karyotype 47,XY,+8, found in 52% of the patient's lymphocytes

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