AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

DOWN SYNDROME: ETIOLOGY, PATHOGENESIS AND PREVENTION

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Abstract: Down syndrome (DS) is a congenital genetic condition characterized by complete or partial trisomy of chromosome 21, accompanied by varying degrees of intellectual disability, congenital malformations of various systems, and additional health problems that affect life expectancy. The article analyzes current information on the etiology of the disease (chromosomal mechanisms: complete trisomy, mosaic and translocation forms), molecular pathogenesis (gene dosage effects and some key genes), clinical features, prenatal diagnostic methods and effective preventive measures (genetic counseling, screening and diagnostic strategies). At the same time, recommendations are given that are relevant to the context of literature and practice in Uzbekistan.

Keywords: Down syndrome, trisomy 21, genetic counseling, prenatal screening. NIPT, Robertson translocation, pathogenesis.

INTRODUCTION

Down syndrome (trisomy 21) is one of the most common chromosomal abnormalities in humans and is one of the most common genetic causes of congenital intellectual disability. It occurs in one in every 700-800 births worldwide; in some countries Depending on socio-demographic conditions, maternal age structure, coverage of prenatal screening programs and population factors, this figure can vary from 1:500 to 1:1200. Although this syndrome was first described in 1866 by the English physician John Langdon Down on the basis of clinical features, its main etiological cause was discovered in 1959 by Lejeune and colleagues as an extra copy of chromosome 21 (trisomy). The morphological and clinical diversity of Down syndrome indicates that it has a profound impact on its developmental processes. The specific phenotypic features that occur in this syndrome are facial morphology, muscle weakness (tendency to hypotonia), growth retardation, intellectual disability, congenital heart defects, digestive system anomalies, endocrine disorders and reduced immunity, all of which are the result of widespread systemic changes associated with the excess number of chromosomes.

Although the genetic basis of Down syndrome is well understood today, the mechanisms observed in it are not limited to a single gene mutation; rather, a complex imbalance in the processes of cell differentiation, embryonic development, and organogenesis occurs due to an increase in the dosage of hundreds of genes located on chromosome 21. In particular, overexpression of genes such as

AMERICAN ACADEMIC PUBLISHER
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DYRK1A, APP, and SOD1 has a significant impact on the formation of neuronal networks, oxidative stress mechanisms, synaptic plasticity, and central nervous system development. Therefore, DS is characterized not only by physical abnormalities, but also by a fundamental disruption of neurodevelopmental processes.

Diagnosis of Down syndrome has improved significantly in recent decades. In addition to traditional ultrasound screening and biochemical tests, non-invasive prenatal testing (NIPT) based on maternal blood mixed with fetal DNA now allows for the detection of trisomy 21 with very high accuracy (up to 99%). Invasive diagnostics (amniocentesis, CVS) provide an accurate diagnosis through chromosome analysis. All of this is important for the family in making the right decisions, managing pregnancy and planning for the future. This disease cannot be completely cured, but early diagnosis, rehabilitation, physical and speech therapy, timely detection and treatment of heart defects, regular monitoring of the endocrine and immune systems can significantly improve the social integration, level of independent living and quality of life of children with Down syndrome. In recent years, social support, special education and inclusion programs for individuals with Down syndrome have been giving effective results in many countries of the world.

ETIOLOGY

The etiology of Down syndrome, that is, its causes, is mainly due to chromosomal numerical abnormalities, characterized by an extra copy of chromosome 21. This extra genetic material has a wide-ranging effect on cellular physiology, embryogenesis, and organogenesis at all stages of human development. Etiological factors manifest themselves in three main forms: simple trisomy (as a result of nondisjunction), chromosomal translocation (Roberson translocation), and mosaicism. Each of these three forms has significant differences in terms of developmental mechanisms, inheritance patterns, risk factors, and clinical consequences.

1. Simple trisomy 21 (95% of cases)

The most common etiological form is simple trisomy. In this case, there are three copies of chromosome 21 instead of two, resulting in 47 chromosomes in each cell. This condition is mainly caused by nondisjunction, that is, the chromosomes do not separate properly during meiosis. In 90-95% of cases, this error occurs in the maternal gamete, because the female egg cells are stuck in the prophase stage for a long time after birth, and over the years, the delicate mechanisms of the separation mechanism can be disrupted due to certain mechanical, epigenetic or intracellular factors.

Nondisjunction can occur during meiosis I or meiosis II:

Meiosis I nondisjunction occurs when homologous chromosomes do not separate, resulting in gametes with 2 chromosomes.

Meiosis II nondisjunction is characterized by the failure of sister chromatids to separate, resulting in the formation of duplicate gametes. As a result, when fertilized by a normal sperm, the zygote has three copies of chromosome 21. This etiological mechanism is not inherited, as nondisjunction occurs randomly.

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2. Roberson translocation (≈ 3-4%)

The translocation form of Down syndrome is when the extra copy of chromosome 21 is not present as a complete chromosome, but rather as a fusion (translocation) with another chromosome. The most common are: 14/21 translocation-21/21 translocation

In this case, the child may have two copies of chromosome 21, but one is attached to another chromosome, creating a functionally higher gene dosage. Translocation carriers are often clinically healthy,because they have a balance of genetic material (balanced translocation). However, the uneven distribution of chromosomes during the formation of sex cells increases the likelihood of having a child with Down syndrome. This form can be inherited, so in such cases it is very important to provide genetic counseling and check the karyotype of the parents.

3. Mosaic form (= 1-2%)

A mosaic zygote is formed with a normal karyotype, but trisomy occurs in some cells due to nondisjunction during mitosis during one of the early divisions of the embryo. As a result, the organism has two different cell lines:

with normal karyotype (46.XX or 46,XY)

trisomy (47,XX+21 or 47,XY+21)

The severity of the mosaic form depends on the proportion of trisomy present in the cells. Milder clinical signs and relatively better intellectual development may be observed, but this is not a strict rule.

4. Maternal age factor in etiology

The most important epidemiological factor associated with Down syndrome is the increasing risk of nondisjunction with age. According to statistics:

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At age 25, the risk is 1:1400, at age 30 - 1:900

At 35 years old 1:350 At 40 years old 1:1000

After 45 years old - up to 1:25

This annual process is associated with a decrease in the function of microtubules in egg cells, kinetochore structures that attach chromosomes, and proteins that control cell division (cohesin, shugoshin).

5. Father's age and rare errors in male gametes

Although the role of the father is much less common (approximately 5% of cases), increasing paternal age may slightly reduce chromosomal stability during spermatogenesis. However, this factor is not considered to have major clinical significance in etiology.

6. The role of exogenous (external) factors

Experimental studies have shown that certain environmental factors, such as radiation, toxic substances, Pesticides and heavy metals have been shown to indirectly affect the meiotic process, but a direct causal relationship with Down syndrome has not been clinically proven. Therefore, DS is considered to be primarily a disease related to intrinsic genetics.

7. Hereditary risk factors (translocational form)

The risk in translocation carriers is as follows:

The risk is 10-15% if the mother is a 14/21 translocation carrier.

Risk if father is a carrier = 2-3%

21/21 translocation risk 100% (all fetuses develop trisomy)

This etiological form is much rarer, but since the family genetic issue is of paramount importance, karyotype examination is always recommended.

PATHOGENESIS

The pathogenesis of Down syndrome is associated with the presence of an extra copy of chromosome 21, which leads to an imbalance in gene dosage in the body, disruption of the process of cell division, disruption of embryonic development, and the occurrence of many systemic functional changes. The pathogenesis is complex and develops through several basic molecular and physiological mechanisms. These processes are described step by step below.

1. Increased gene dosage - the main mechanism of pathogenesis

At the heart of the pathogenesis of Down syndrome is the overexpression of genes on chromosome 21. Under normal conditions, each gene is present in a normal amount, which maintains protein synthesis and cellular function in balance. In trisomy, due to the increase in the number of genes, protein synthesis increases and: the cell cycle; embryonic development; metabolic processes; neuronal connections, oxidative stress mechanisms are disrupted. Chromosome 21 contains more

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ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

than 300 genes, of which 30-40 play a primary role in the development of the Down syndrome phenotype. Down syndrome is caused by the presence of three copies of chromosome 21 (trisomy) in a human cell. The main cause of this condition is that the chromosomes do not divide correctly during the formation of an egg or sperm (meiosis). As a result, a child is born with 47 chromosomes instead of 46.

What happens in the brain and nervous system?

The brain size becomes smaller, especially the front and lateral parts do not develop.

The number of neurons (brain cells) decreases, and their interconnections (synapses) develop very slowly.

Dendrites (neuron branches) are short and poorly branched, which is the main cause of mental retardation.

Almost everyone over the age of 40 develops Alzheimer's disease because the amyloid-producing gene is located on chromosome 21 and is activated three times more often.

In the heart

More than half of all children have congenital heart defects. The most severe are:

atrioventricular canal defect (complete absence or large hole in the wall between the ventricles and atria),

ventricular septal defect (VSD),

atrial septal defect (ASD),

In the endocrine system

Hypothyroidism (underactive thyroid) is very common, occurring in 10-50% of cases.

Diabetes and autoimmune thyroiditis are also often associated.

Changes in appearance and skeleton

Height is very short (average 140-160 cm in adults).

The head is small, with a flat back (brachycephaly).

The eyes are slanted, with a skin fold (epicanthus) at the inner corner.

The nose is flat, the tongue is large and protruding, with a cleft.

The fingers and toes are short, and the little finger is curved inward (clinodactyly).

The neck is short and has a lot of skin folds on the back.

There is instability between the first and second cervical vertebrae, which puts children at high risk of spinal injuries when they play sports. Nowadays, with proper care, heart surgery, hormone

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therapy, special education, and rehabilitation, people with Down syndrome can live to be 60-70 years old. In the past, most people didn't even make it to 10-20 years old.

The main problem is the overactivity of more than 300 genes due to the extra chromosome 21, which disrupts the development of the entire organism. So far, this disease cannot be completely cured, but only the symptoms can be alleviated and the quality of life improved.

Diagnostics

Down syndrome is detected both during pregnancy and after birth.

1. During pregnancy (prenatal screening and diagnosis)

Weeks 11-14: Ultrasound shows. Blood test (PAPP-A and ß-hCG) indicates high risk

Weeks 15-20: triple or quadruple test (AFP, hCG, estriol, inhibin-A).

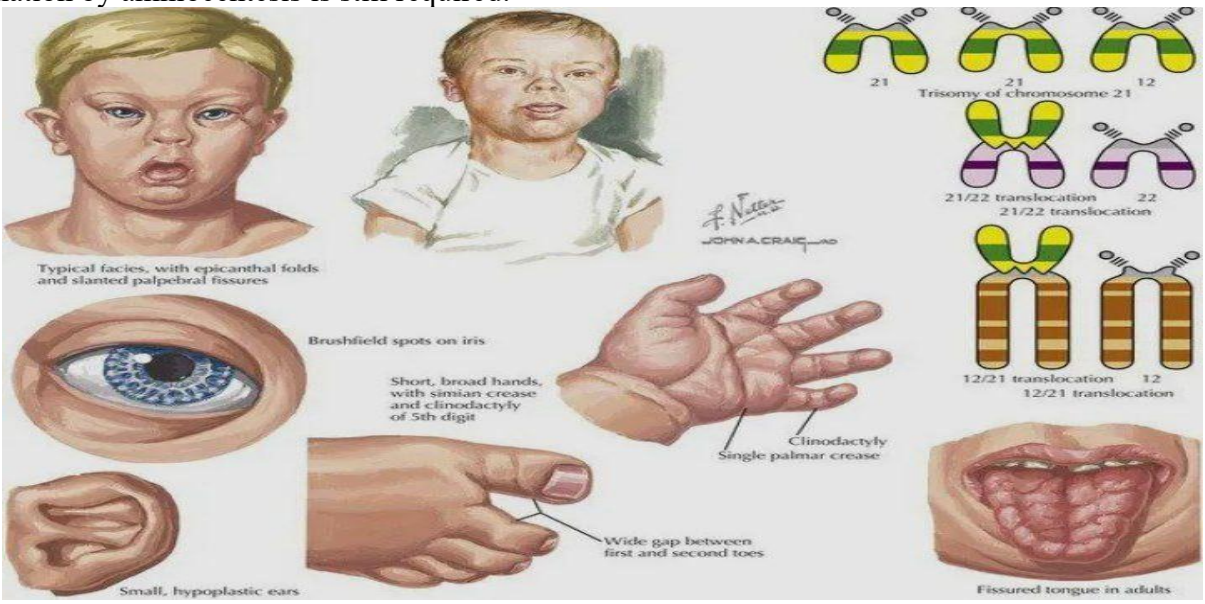
The most accurate methods (give 100% correct answers)

Chorionic villus sampling (weeks 10-13)

Amniocentesis (15-20 weeks)

Cord blood sampling (cordocentesis, after 18 weeks)

These are used to check the karyotype of the child's cells → it is written as 47,XX,+21 or 47,XY,+21. A new and safe method (since 2012): fetal DNA from the mother's blood (NIPT - non-invasive prenatal testing). It shows Down syndrome with 99.9% accuracy from the 10th week, but confirmation by amniocentesis is still required.



2. After birth (postnatal diagnosis) The doctor suspects childbirth (external signs are very characteristic); flat face, slanted eyes, large tongue, short neck, one line on the palm (simian line), etc. A definitive diagnosis can only be made by karyotype analysis:

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Blood is taken from a newborn baby and the result is 47,+21 within 3-7 days.

Treatment: Down syndrome itself (the extra chromosome) cannot be eliminated with any medication or surgery at this time. Treatment is aimed only at relieving symptoms and improving quality of life. Regular monitoring and treatment directions: Heart Surgery: In cases of heart defects (50-60% of cases), open heart surgery is performed between 3-12 months of age. If successful, the child will live a normal life. Thyroid gland (hypothyroidism) A blood test for TSH and T4 is done every year. If there is hypothyroidism, L-thyroxine (Eutirox, L-thyroxine) is taken for life - very simple and effective,

Hearing and eyes: Ear doctor (ENT) and audiometry every 6 months. Eye doctor 1-2 times a year (strabismus, cataracts, glasses).

Immunity and infections

Even a common cold can turn into pneumonia. Antibiotics and vaccinations (pneumococcus, flu) are often required.

Leukemia screening

From 1 to 5 years of age, a complete blood count every 6-12 months to check for signs of leukemia.

Cervical spine instability

At the age of 3-5, an X-ray or MRI of the cervical spine is performed. If there is Atlanta-axis instability, sports (gymnastics, jumping, football) are prohibited, sometimes surgery is performed.

Development support (most importantly!

0-3 years: Tomorrow's Development Program (Vojta, Bobat, Sensory Integration)

Speech therapist (logopedist) speech development

Defectologist and special educator reading, writing, social skills

Chiropractic, massage, physical therapy - normalization of muscle tone

In adulthood

Alzheimer's symptoms may begin at the age of 30-35, with memory loss and loss of self-control.

In such cases, medications such as neuroleptics, memantine, and donepezil are prescribed.

Result

If all the above measures are implemented in a timely and correct manner, people with Down syndrome can now live in Uzbekistan to the age of 60-70, study, work (simple jobs), live independently, or start a family (men often suffer from infertility, while women have a 50% chance of having children). The main thing is early diagnosis, constant medical supervision, and patience on the part of parents.

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Prevention

The possibility of specific "prevention" (primary prevention) of Down syndrome is limited:

Trisomy is caused by a meiotic error, and it is not yet scientifically proven that these errors can be reliably prevented by lifestyle or simple medications. However, the following preventive strategies are widely used:

1. Genetic counseling (reproductive counseling): first of all, if a translocation carrier is identified in the family, professional genetic counseling is necessary - this will inform the parents about the risk of recurrence, options (PGT, prenatal diagnosis) and reproductive choices. If either parent is a balanced translocation carrier, the risk of DS in subsequent fetuses is significantly increased.

2. Prenatal screening and diagnosis: Offering screening in all pregnancies (ACOG recommendation) and offering NIPT or invasive diagnosis when high risk is identified is considered "secondary prevention" (and scientific and practical prevention), as early detection allows the family the opportunity for planning and psychological preparation.

3. Assisted reproductive technology and PGT (preimplantation genetic testing): if the parent is a translocation carrier or there is a high risk of recurrence of a previously born child with DS, in vitro fertilization (IVF) and PGT are used to select chromosomally normal embryos and implant the fetus This can be done. This is considered a reproductive choice.

4. Public and medical education: Educating the general public about the impact of maternal age, reproductive planning, and prenatal screening options can improve population-level approaches to DS. (Not directly “preventing” but has the potential to control the epidemiological profile.

Summary

Down syndrome A complex genetic condition associated with a triplication of the 21st chromosome. The etiology is clear (trisomy, translocation, mosaicism), the pathogenesis is based on excess gene dosage. Clinical and social aspects require an integrated approach: prenatal screening and diagnostics, genetic counseling, multidisciplinary management and rehabilitation. It is important to develop genetic counseling and prenatal diagnostics as the main preventive measure. The importance of Down syndrome in medical practice is determined not only by the defect at the genetic level, but also by its social, psychological and rehabilitation aspects. Today, the widespread use of prenatal screening technologies, in particular, first-trimester ultrasound, biochemical tests, non-invasive prenatal DNA tests (NIPT), makes it possible to detect the syndrome in the early stages of pregnancy. Invasive diagnostics chorionic biopsy, amniocentesis and cordocentesis also remain the gold standard. This allows for early detection of the disease, comprehensive genetic counseling of the family, assessment of the state of fetal development and scientific justification for making important decisions. yet

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