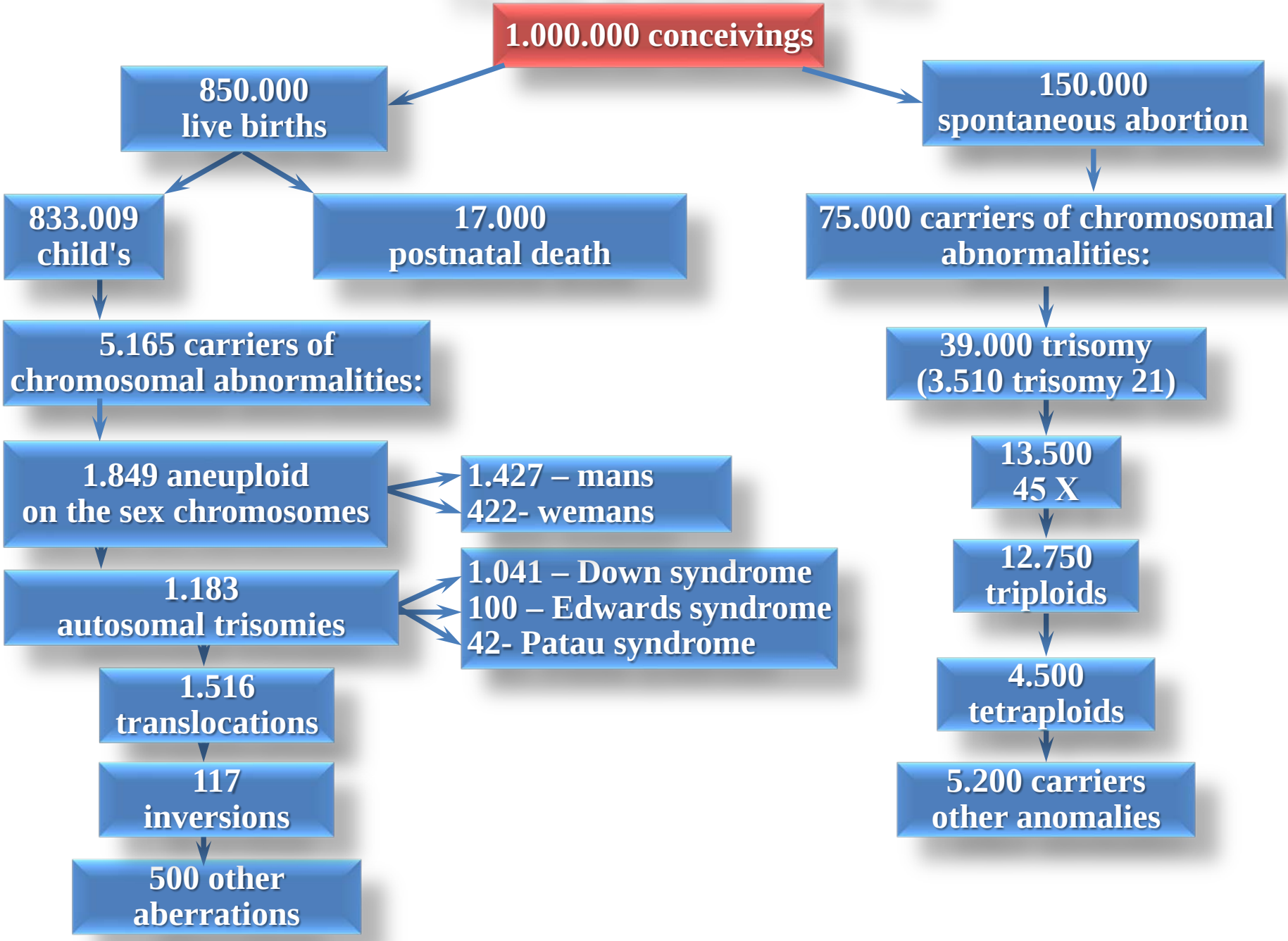
Lecture 3d

Chromosomal human diseases

The Fate of conceiving in Man



HEREDITARY DISEASES –

PATHOLOGICAL STATES OF THE ORGANISM FOR THE CHANGE OF THE GENETIC MATERIAL (MUTATION)

three groups of diseases with different mechanisms of initial damage

- **CHROMOSOMAL SYNDROME**
- **MONOGENIC DISEASES**
- **MULTIFACTORIAL (with hereditary predisposition)**

CHROMOSOME SYNDROME

It is described ≈ 1000 anomalies,

≈ 100 - available for clinical diagnosis

CAUSE: Changing the number and / or structure of chromosomes (random mutations - de novo).

Chromosomal syndromes are not inherited!

In the overwhelming majority of cases, chromosomal syndromes are observed with meiotic disruption of chromosomal divergence in women. This is due to the fact that all the eggs are laid in the female fetus.

In the process of growth and maturation of a girl to an adult woman, the eggs grow old and therefore errors accumulate in their genome.

Whereas in men spermatozoa are updated about every two weeks and therefore spermatozoa new generation, as a rule, does not contain any errors in the genome.

DIFFERENT :

GENOMIC SYNDROME
(changes in the number of chromosomes)
CAUSE:
Infringement meiosis at parents (nondisjunction of chromosomes), Crushing of the zygote.

STRUCTURAL ABERRACTIONS
(changes in the structure of the chromosome)

- ✓ **cat's scream syndrome (46, XX, 5p-),**
- ✓ **Orbeli syndrome (46, XУ, del.13p-)**

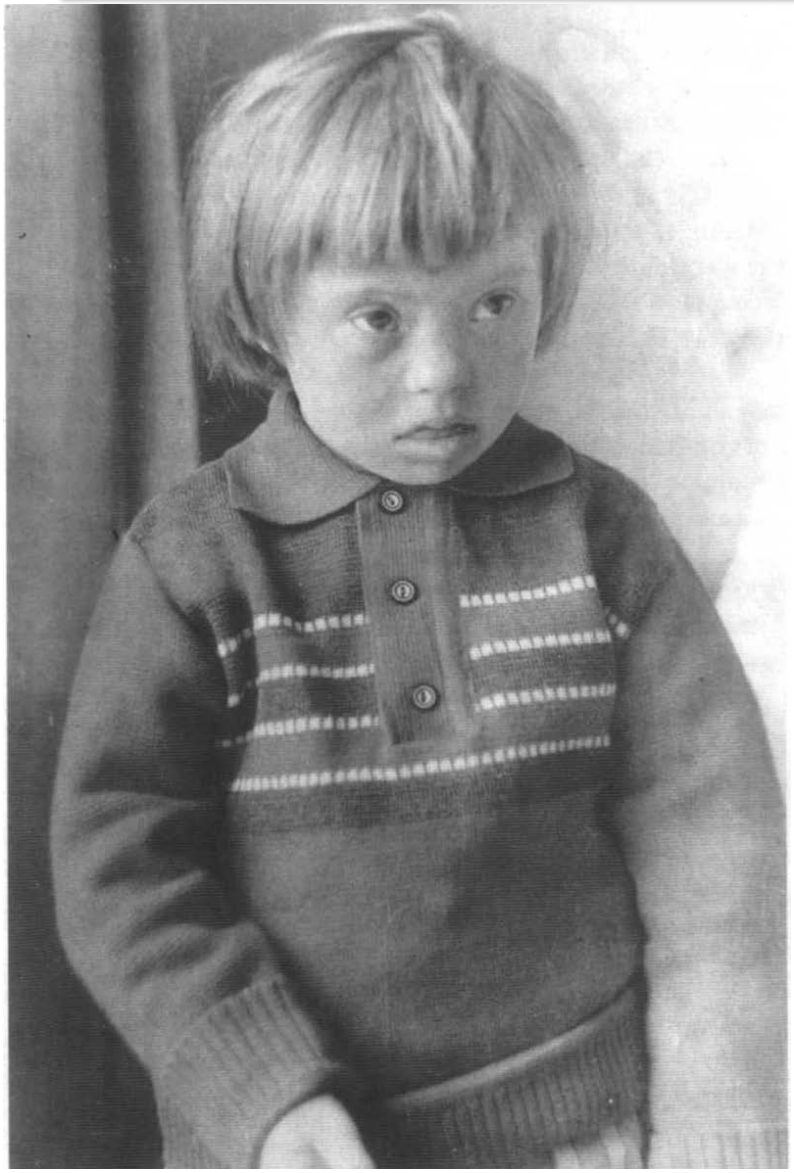
Changes in the number of autosomes

- ✓ **from. Down,**
- ✓ **from. Patau,**
- ✓ **from. Edwards et al.**

Changes in the number of sex chromosomes

- ✓ **Shereshevsky-Turner,**
- ✓ **Klinefelter,**
- ✓ **Trisomy -X**

Down Syndrome



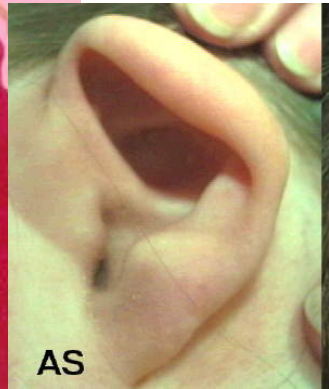
Trisomy 21

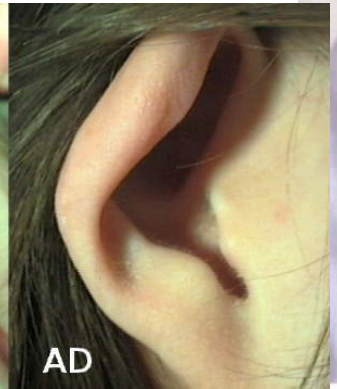
1: 1000

Down syndrome equally affects both girls and boys, the disease has no ethnic distribution and is found everywhere.

60th years of the twentieth century
Masha T. 6 years old
Down syndrome (brachymorphic physique, flat face, Mongoloid eye section, large tongue, mental retardation)

SYNDROME DOWN
(Trisomy 21 chromosomes)





Kennedy, 10 years old (USA)

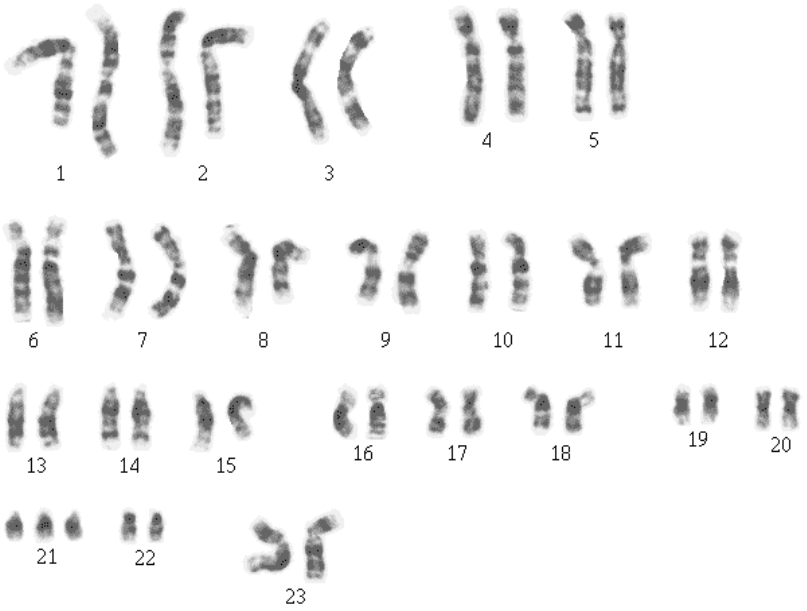
Luciano, 1 year (Argentina)

Saira, 6 years old (India)

Julianna, 13 years old (Germany)

NOW
Everything is not so bad if properly treated and educated

http://www.woman.ru/kids/medley5/article/193151/?startLeaflet=2#8



Object of investigation: fetal umbilical cord blood.
Fetal karyotype: 47XX + 21 (Down's syndrome)

The age of the future mother influences the risk of developing Down syndrome in a child, the probability of forming this pathology is:

from 20 to 24 years - 1: 1562;

25-35 years - 1: 1000;

35-39 years - 1: 214;

over 45 years, the risk increases to 1: 19.

The father's age at the risk of birth affects after 42 years.

Diagnosis of Down syndrome in the first trimester is a combined screening analysis that determines the risk of developing this pathology in the fetus.

The study is conducted strictly in the period from 11 to 13 weeks and 6 days of pregnancy.

1. Determination of the level of β-subunit of chorionic gonadotropin (pregnancy hormone hCG) in the venous blood of the mother. With this chromosomal pathology of the fetus, an elevated level of the β-subunit of CG more than 2MoM will be determined;

2. Determination of the level of PAPP-A protein-A plasma of a pregnant woman, associated with pregnancy. The high risk of the syndrome is associated with a PAPP-A index of less than 0.5MoM;

3. Determination of the thickness of the collar space with the help of ultrasound of the fetus. With Down syndrome, this figure is more than 3 mm.

With a combination of the three described indicators, the probability of Down's syndrome in a fetus is 86%.

Diagnosis of Down's syndrome in the second trimester is conducted between 16 and 18 weeks.

Determining the level of hCG in the blood of a pregnant woman - with Down's syndrome, the figure is higher than 2MoM;

Determination of the level of a-fetoprotein in the blood of a pregnant woman (AFP) - with Down's syndrome, the indicator is less than 0.5MoM;

Determination of free estriol in the blood - less than 0.5MM is characteristic of Down's syndrome;

Determination of inhibin A in the blood of a woman - an indicator of more than 2MoM is characteristic of Down syndrome;

MoM – multiple of median

Fetal ultrasound:

A) smaller size of the fetus relative to the norm for a period of 16-18 weeks;

B) shortening or lack of nasal bone in the fetus;

C) reduction of the size of the upper jaw;

D) shortening of the humerus and femur bones of the fetus;

E) an increase in the size of the bladder;

E) one artery in the umbilical cord instead of two;

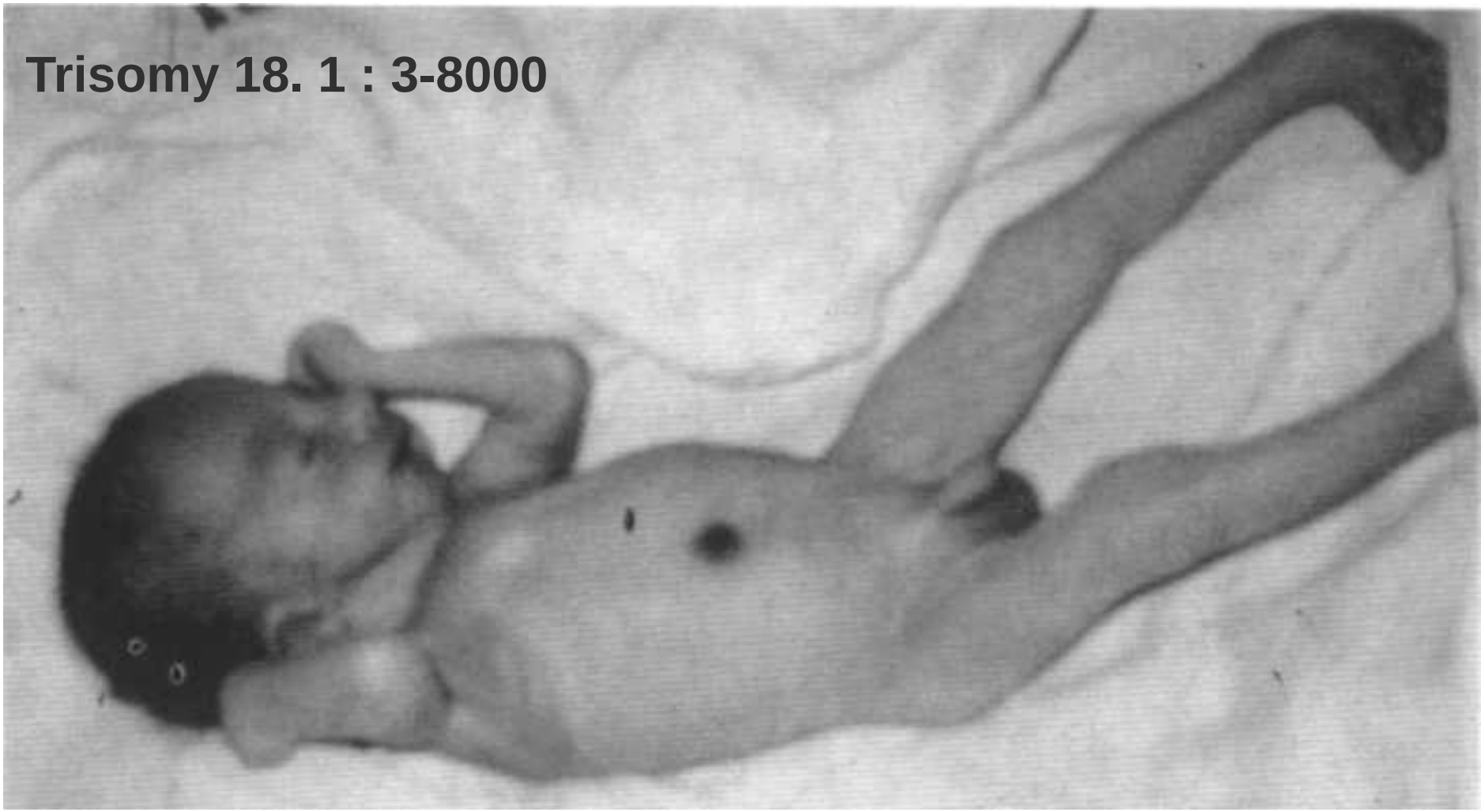
G) lack of water or lack of amniotic fluid;

H) palpitations in the fetus.

When all the signs are combined, the woman is offered invasive diagnostics for genetic research: transabdominal aspiration of the placenta villi; transabdominal cordocentesis with puncture of the umbilical cord.

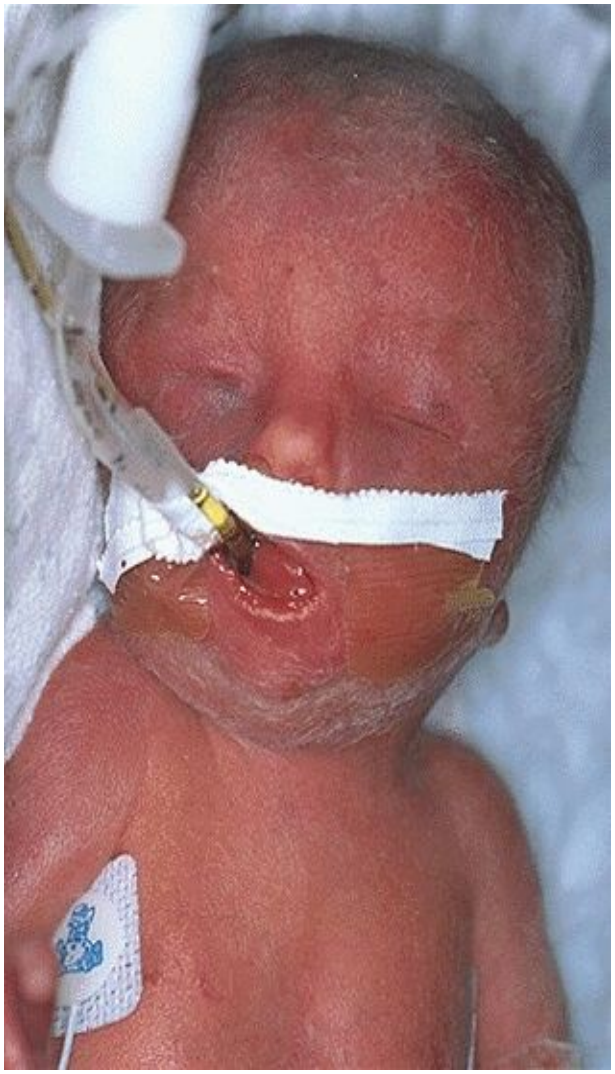
Symptoms of Down's syndrome in a newborn: a shortened skull;
small head size;
wrong shape of the ears;
flattened facial skull;
saddle nose;
flat nose bridge;
small mouth;
small chin;
thick, sulcate tongue;
oblique incision of eyes;
open mouth;
skin folds located at the inner corners of the eyes;
short neck;
a skin fold on the neck;
short upper and lower limbs;
short fingers;
flattened wide palms;
horizontal fold on the palms;
concave form of little fingers;
visible distance between the first and second toes;
weak muscle tone.

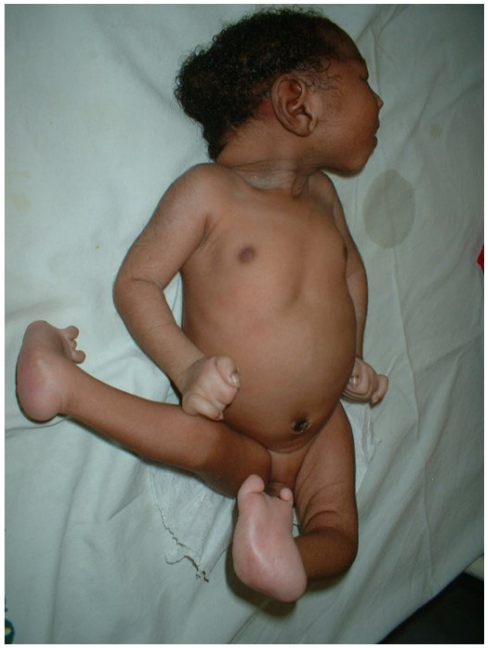
Edwards Syndrome

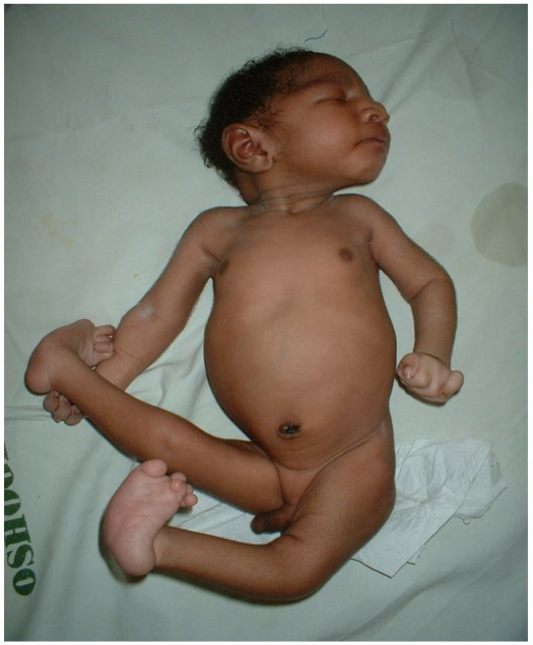


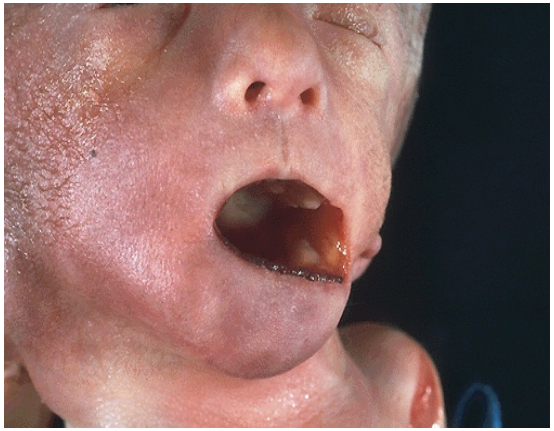
Vitya M., 1 month Diagnosis: Edwards syndrome (hypotrophy, dolichocephaly, small lower jaw, short eye cracks, muscular hypertonia, club foot)

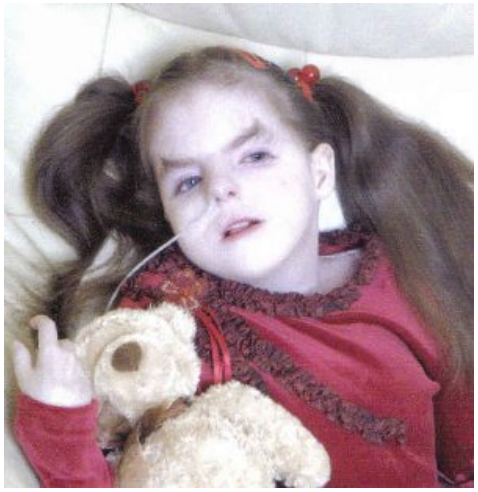
Appearance of a patient with Edwards syndrome











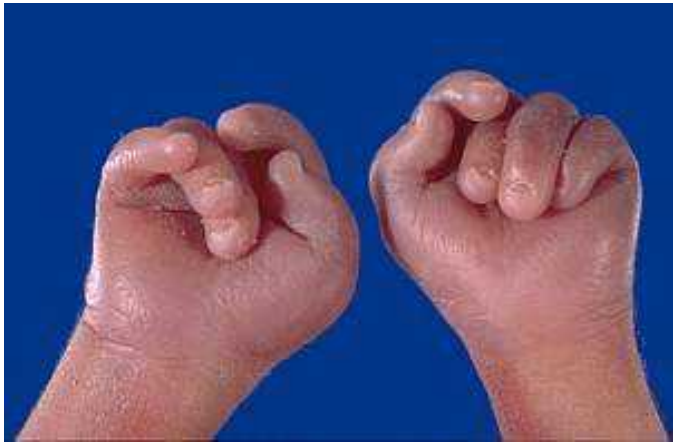
In girls this disease occurs 3 times more often.
The risk of Edwards syndrome increases significantly if the pregnant woman is 30 or more years old.
Prenatal diagnosis of this syndrome is carried out in 2 stages:
At the time in A) 8-12 weeks, biopsy of chorionic villi, B) 11-13 weeks definition of fetal karyotype in pregnant women at risk; C) in the woman's blood, the level of human β-chorionic gonadotropin and plasma protein A is determined. Then, taking into account these data, the age of the pregnant woman is calculated the risk of having a child with Edwards syndrome, and a risk group of pregnant women is formed.
In 14-18 - amniocentesis (study of amniotic fluid), after 20 weeks - cordocentesis (intrauterine blood sampling from the umbilical cord with ultrasound control). After this, the presence or absence of an additional 18th chromosome is determined in the obtained material by means of KF-PCR (quantitative fluorescent polymerase chain reaction).
If the pregnant woman has not undergone a genetic screening test, then at a later date, the preliminary diagnosis of Edwards syndrome is performed using ultrasound.
Other indirect signs on the basis of which it is possible to suspect Edwards syndrome on later terms: The presence of anomalies of the development of bones and soft tissues of the head ("wolf mouth", microcephaly, low landing of ears, "hare lip", etc.). Detection of defects from the cardiovascular, urogenital system, as well as the musculoskeletal system.

After the birth of the child, the basic diagnostic features of the presence of Edwards syndrome are the following:

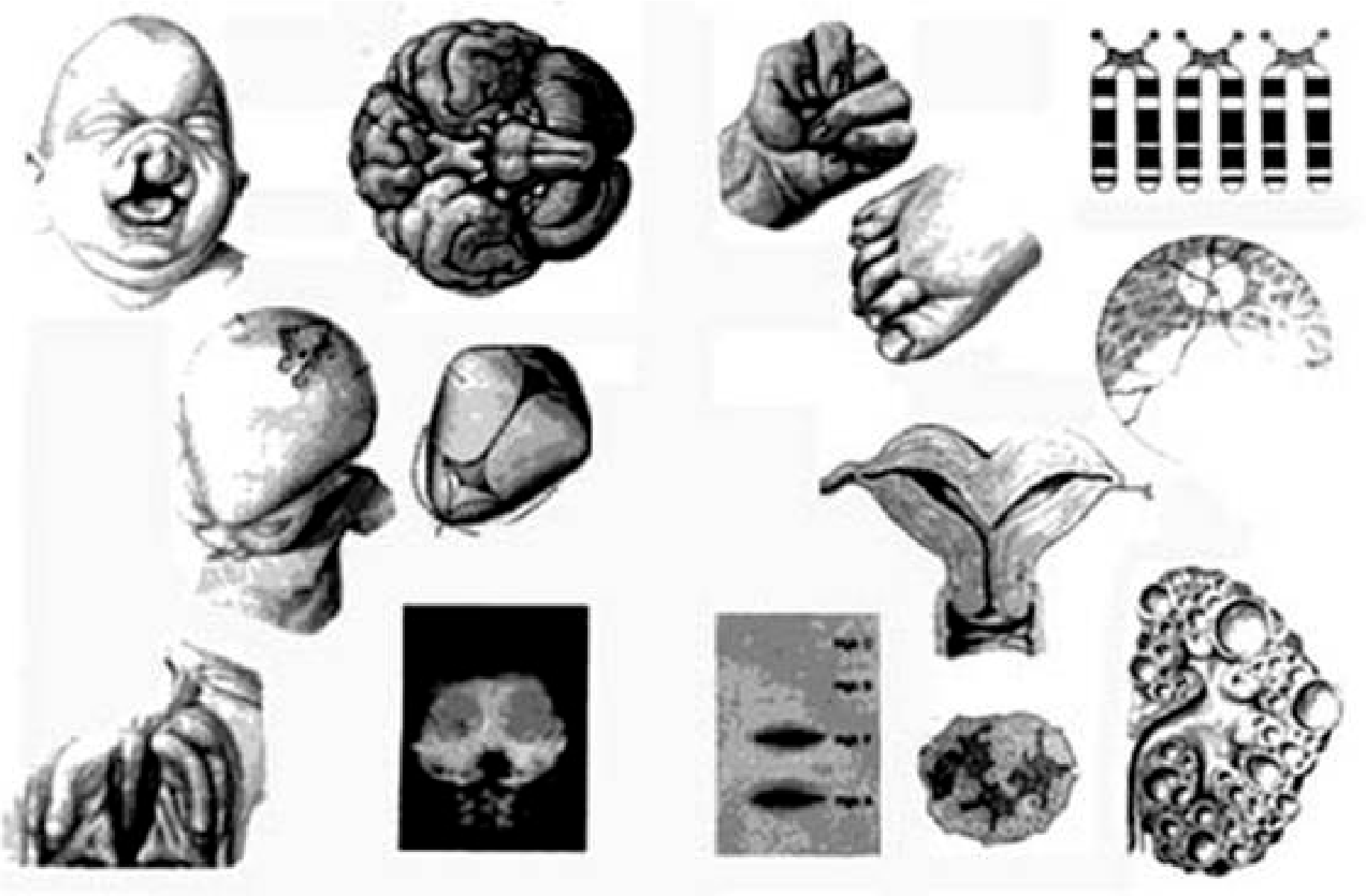
Microcephaly, low birth weight Having a "hare lip" or "wolf mouth"

Signs of a characteristic dermatographic pattern: undeveloped on the fingers of the distal flexion fold, the presence of a transverse palmar sulcus on the finger pads in 1/3 of the cases, the change in the palm skin pattern: the distal arrangement of the axial triradius and the increase in the ridge count.

Further, the diagnosis is confirmed by the definition of the karyotype of the child using the KF-PCR method.



Syndrome Patau



Trisomy 13

1: 7000-10000;

the sex ratio is approximately the same

The smaller part of cases of the Patau syndrome is represented by unbalanced translocations of chromosomes of the 13th pair, mosaic forms, isochromosome.

Congenital malformations of the brain, facial and brain parts of the skull, eyeballs.

Newborns with the Patau syndrome have a characteristic appearance: microcephaly, often - trigonecephalus; Low, slanting forehead, narrow eye slits; flat, sunken bridge of the nose, "wolf mouth" and "hare's lip," low position and deformation of the auricles.

Disorders from the central nervous system include holoprozenzepaliyu, cerebellar hypoplasia, hydrocephalus, dysgenesis of the corpus callosum, spinal hernia (meningomyelocele). Children with Patau syndrome always have deep mental retardation in the degree of idiocy, they lag far behind their peers in physical and mental development.

Deafness, microphthalmia, congenital cataract, colobomas, retinal dysplasia, optic nerve hypoplasia are frequent manifestations of Patau's syndrome.

Anomalies of internal organs in the Patau syndrome can be represented by various combinations: congenital heart defects, kidneys, digestive system.

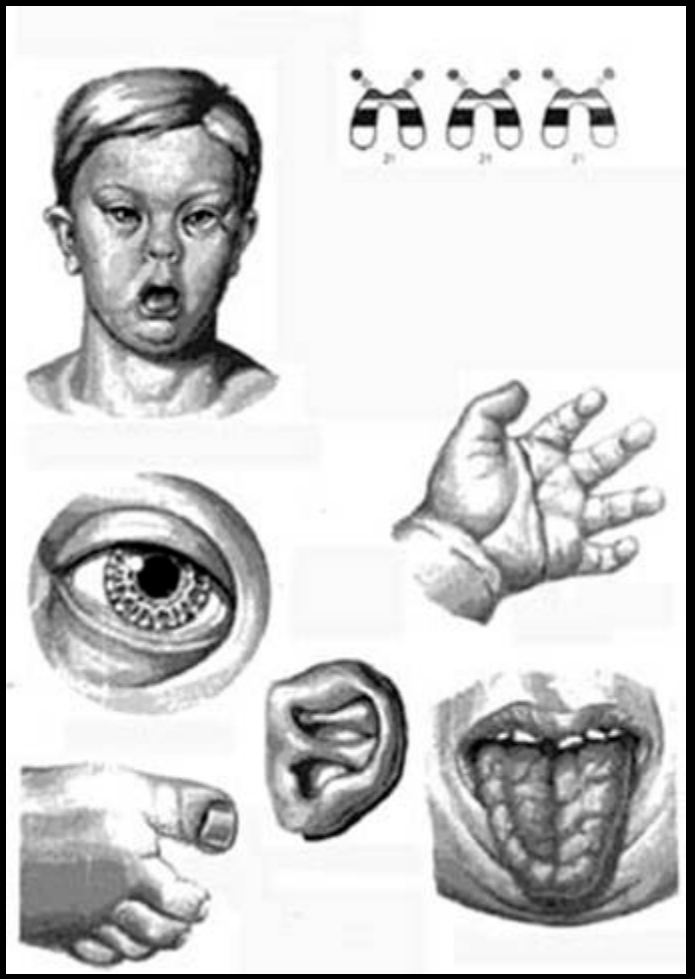
Disturbances in the development of the musculoskeletal system are characterized by the polydactyly of the hands and feet, syndactyly, the flexor position of the hands, the "foot-rocking", the presence of the embryonic umbilical hernia. In boys with the syndrome of Patau, cryptorchidism, hypospadias is observed;

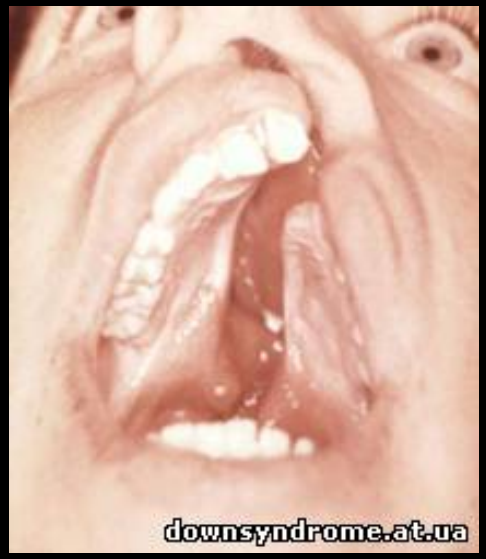
Girls have hypertrophy of the clitoris and labia, doubling of the uterus and vagina, bicorne uterus.

Prognosis: an unfavorable 95% of patients die in the first year of life.

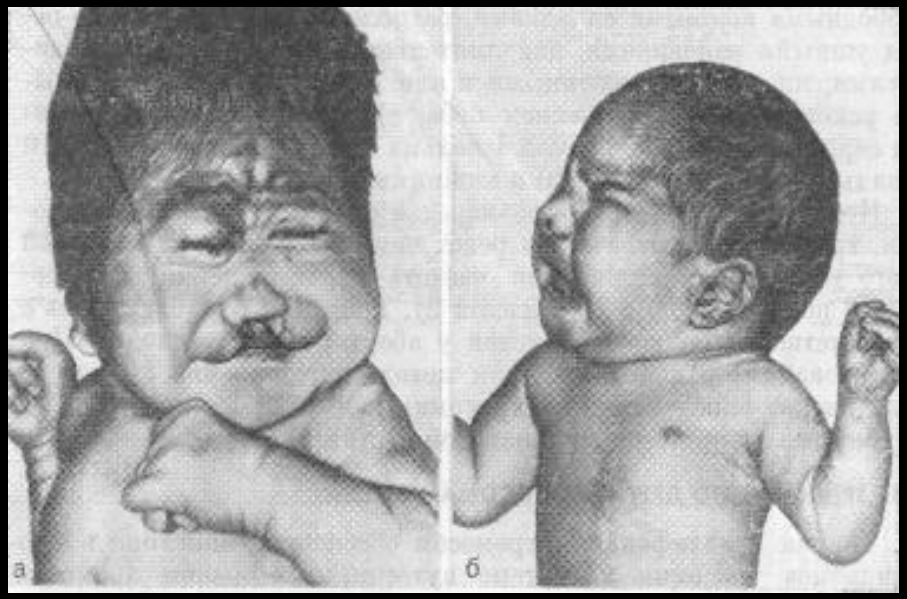
In developed countries, the number of children under 5 years old does not exceed 15%, up to 10 years - 2-3%.

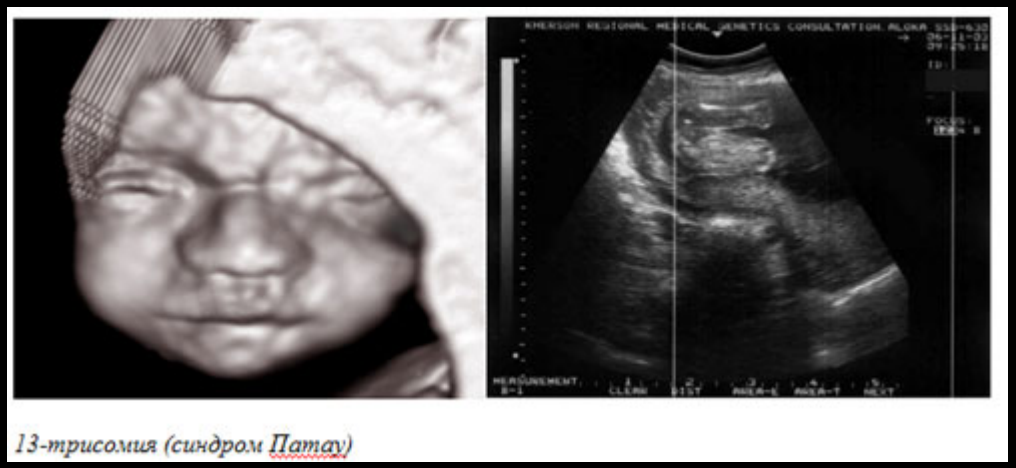
Appearance of the patient with the Patau syndrome:



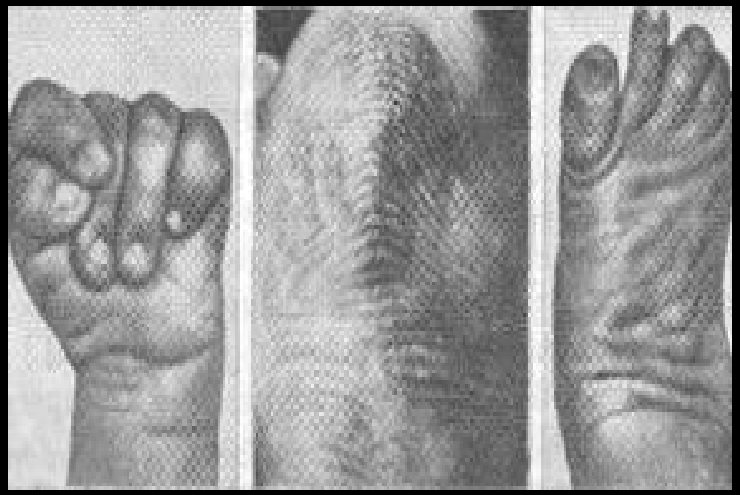


Appearance of the patient with the Patau syndrome:





13-трисомия (синдром Патау)



S. Shereshevsky - Turner

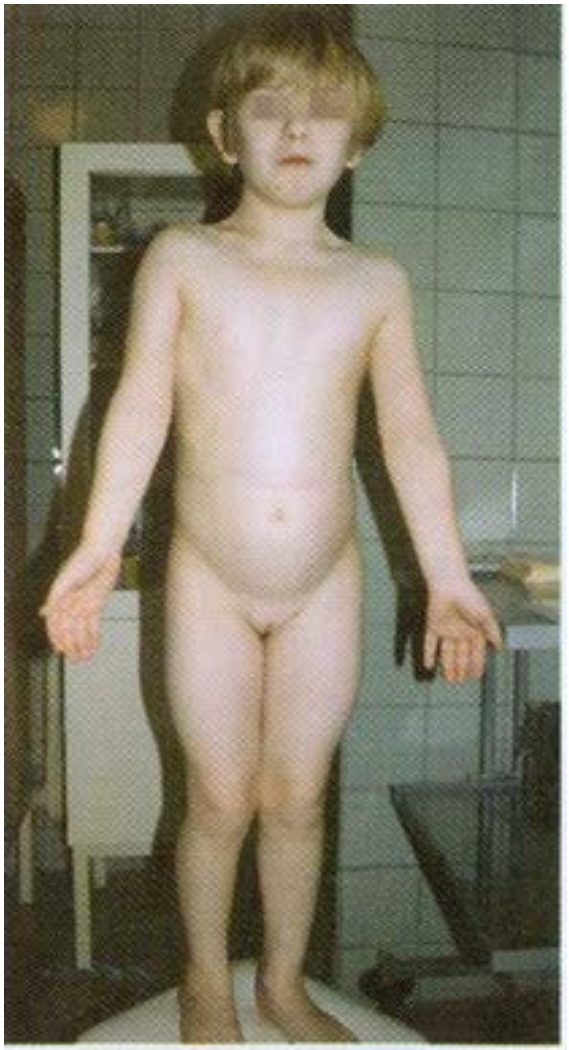
1: 1500 births less

44 X,

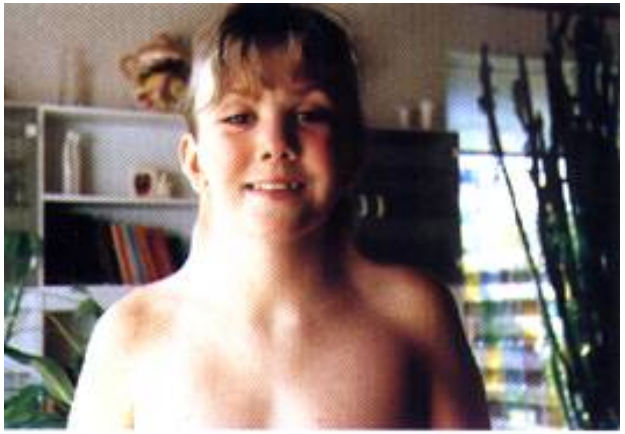
or 45 X, but with deletions on the second X chromosome,

very rarely 45 Y with deletions in

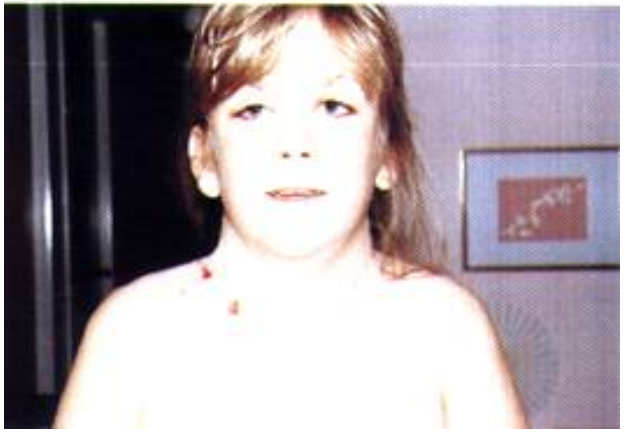
X chromosome

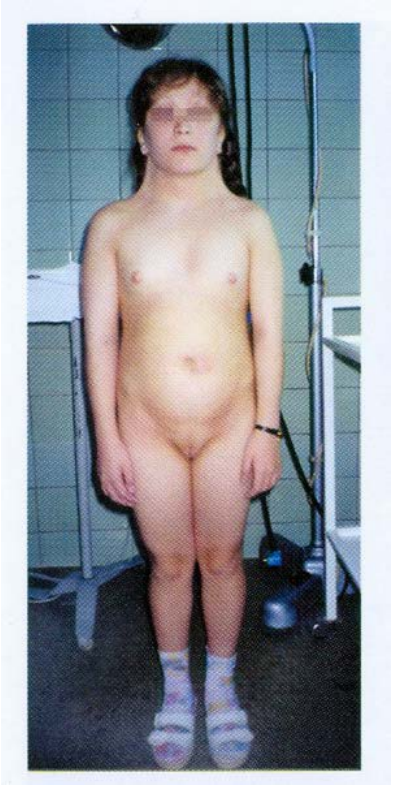


She is 13 years old. Syndrome Shereshevsky-Turner.
Low growth, absence of secondary sexual characteristics.



Skin folds in the neck are a characteristic symptom of the disease. In the photo: a girl before and after plastic surgery





She is 14 years old.
Syndrome Shereshevsky-Turner.
Pterygopal folds on the neck "head of the Sphinx".

The main clinical signs of Shereshevsky-Turner syndrome are:

- **Low body weight and height of the child with full term pregnancy;**
- **Preservation of low growth as the child develops (as a rule, the growth does not exceed 150-155 cm);**
- **"Neck of the Sphinx" (short neck with pterygoid folds);**
- **Broad chest;**
- **Small low ears;**
- **Curvature of elbow joints;**
- **Short fingers due to shortening of metacarpal bones;**
- **Lymphostasis (swelling) of feet and hands;**
- **Defects of the reproductive system (decrease in the size of the uterus, absence of ovaries, underdevelopment of the clitoris and small labia, hypertrophied large labia, etc.);**
- **Absence or weak severity of secondary sexual characteristics (absence of menstruation, small embolism of pubis and axillae, underdevelopment of mammary glands);**
- **Possible malformations of cardiovascular, urinary and endocrine systems;**
- **Propensity to high blood pressure and obesity.**

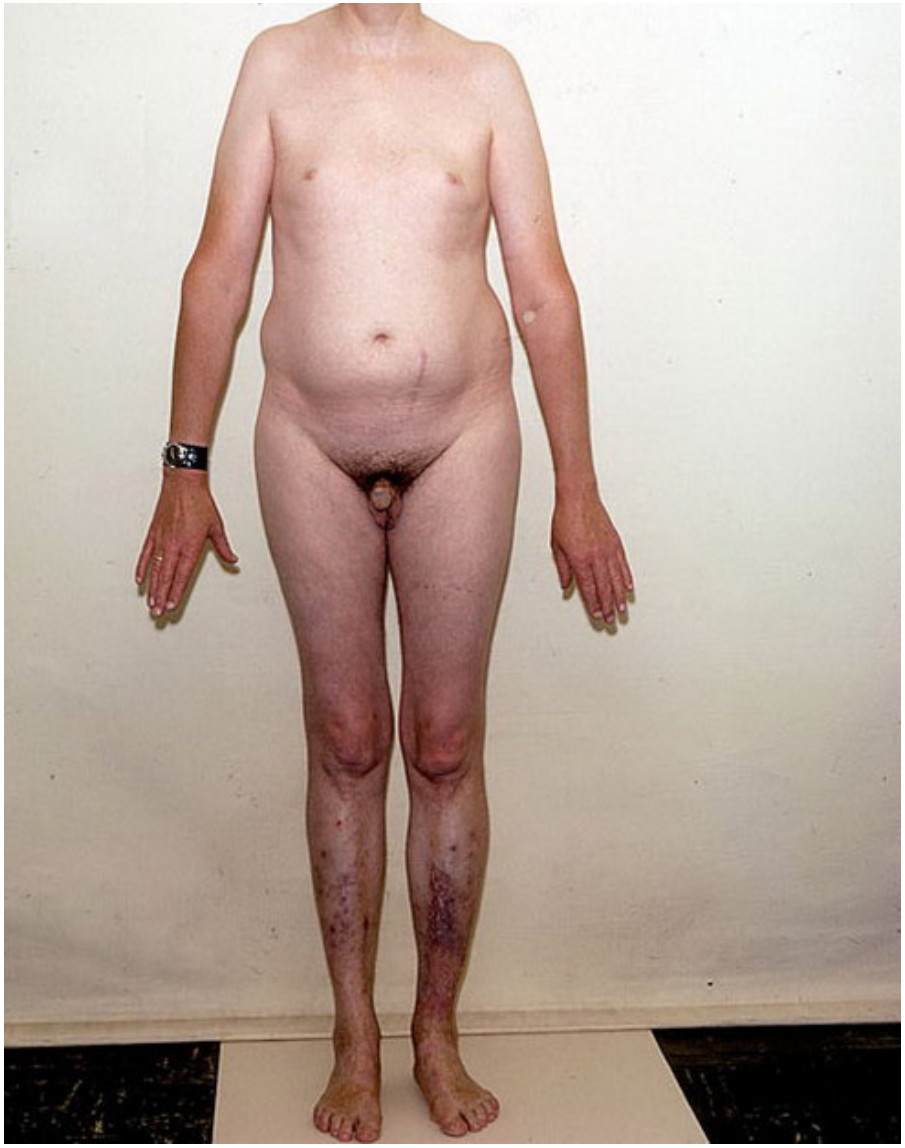
Mental abilities, as a rule, do not suffer.

The main diagnostic measures:

Analysis of blood for hormones (significantly reduced the amount of estrogens and increased levels of FSH and LH);
Definition of a karyotype, consultation of a geneticist;
Consultation of obstetrician-gynecologist;
Ultrasound of the pelvic organs;
Consultation of narrow specialists as necessary;
Additional survey methods for detecting developmental defects by indications.

Klinefelter's syndrome

1 : 500 — 1 : 600



By the number of additional X-chromosomes, several types of this syndrome are distinguished:

One additional chromosome (karyotype 47XXY). This species is classical, occurs most often;

Two additional chromosomes (karyotype 48XXXY);

Three additional chromosomes (karyotype 49XXXXU);

One additional X chromosome and one extra Y chromosome (karyotype 48XXYY);

Mosaic form (additional X-chromosome is only part of the body cells). Karyotype 46XY / 47XXY.

Early manifestations of the syndrome

Favorable course of pregnancy, which distinguishes this disease from other chromosomal diseases;

High growth (significant increase in age after 5 years);

Disproportionate physique (long legs, high thin waist);

Minor delay in speech development;

Possible difficulties in the perception of the material by ear.

Most signs of the disease appear in adolescence:

Gynecomastia (enlargement of mammary glands, persisting for a long time);

Androgenic insufficiency caused by gradual atrophy of testicles (meager vegetation on the body and face, spleen on the female type, full absence of spermatozoa, overweight, decreased testicles). At a more mature age (after 25 years), men often complain about decreased sexual desire and impotence;

High growth (above 180 cm), long legs.

Intellectual and mental development:

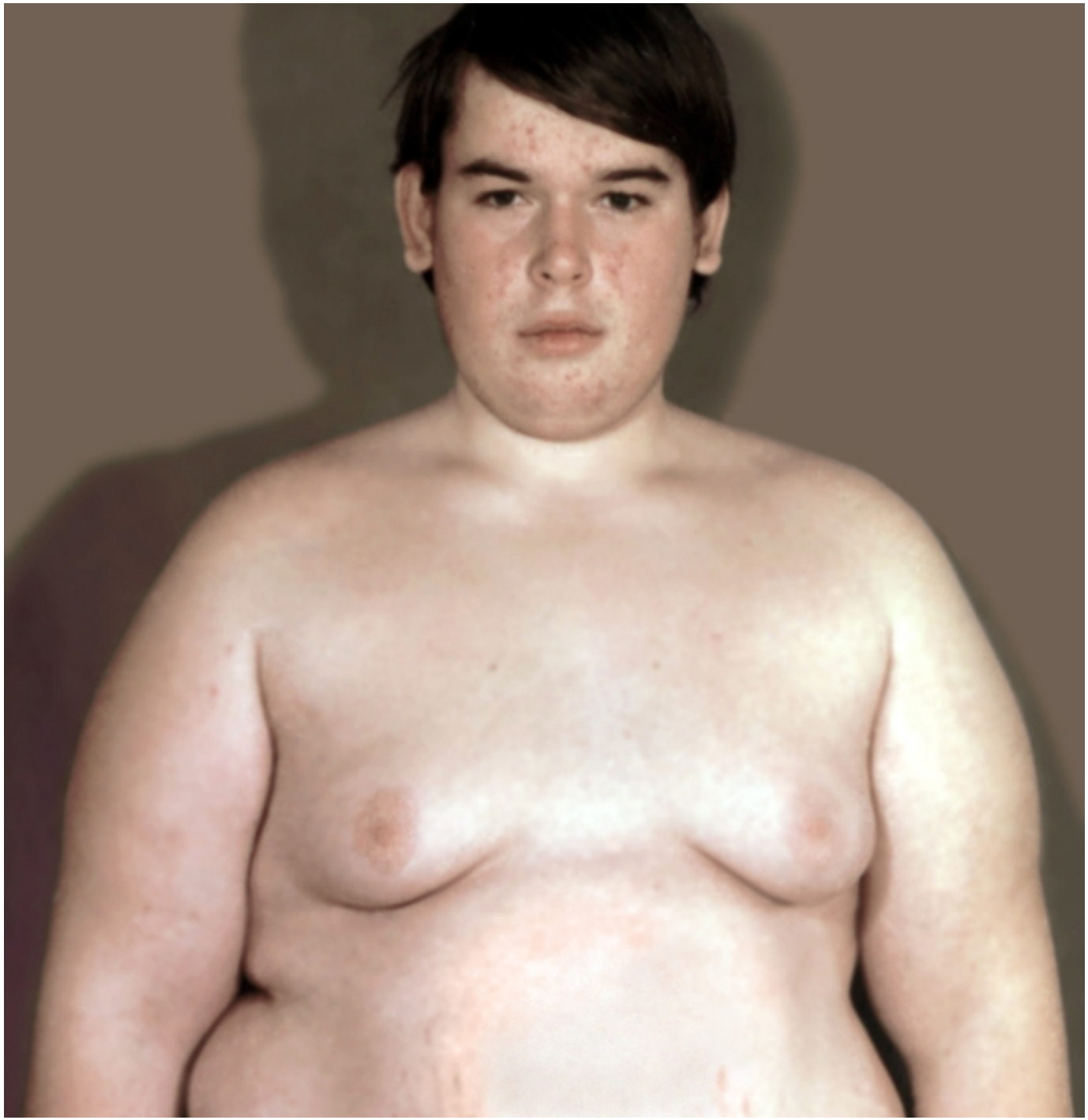
The coefficient of intelligence is variable: from medium to high level;

Possible difficulties with hearing large volumes of material;

Difficulties with the construction of long grammatical phrases;

Propensity to low self-esteem, increased sensitivity;

Propensity to alcoholism and drug addiction (not exactly proven).



Variants of the disease

One additional X-chromosome and Y-chromosome (karyotype 48XXYY):

High growth (185 cm and above);

Decreased intelligence, slow speech;

Propensity to depressive states and increased aggression;

Difficulties in social adaptation.

Variants of the disease

Two additional X-chromosomes (karyotype 48XXXУ):

Growth varies from medium to high;

Frequent malformations (fusion of the ulnar and radial bones, flat nose, increased distance between the eyes, etc.);

The variability of the intellect from medium to mild mental retardation;

Apathy, infantilism, aggression is often absent.

Three additional chromosomes (karyotype 49XXXXU) (extremely rare form):

Low growth;

Frequent cases of congenital malformations (heart defects and large vessels, wolf mouth, hare lip, joint deformities, small size of testicles and penis);

Decreased intelligence in the form of mental retardation (from mild to severe degrees);

Possible attacks of aggression, the rest of the time are calm and friendly.

Variants of the disease

Mosaic form (karyotype 46ХУ / 47ХХУ):

Weakness of all symptoms of classical form;

The preserved possibility of fertilization (oligospermia).

Trisomy X syndrome

44XXX

1 : 900-1000

Described by Jacob in 1959, 44XXX

There are options for 44XXXX and 44XXXXX.

Underdeveloped ovaries,

Hypoplasia of the uterus,

Irregular menstrual. cycle,

Infertility (in 70%),

A slight decrease in intelligence,

Psychoses

Speech delays,

Dyspraxia,

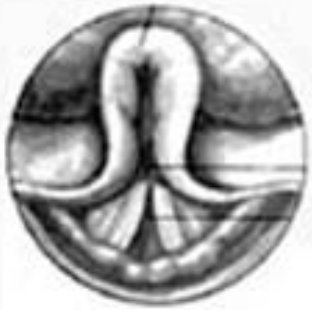
High growth,

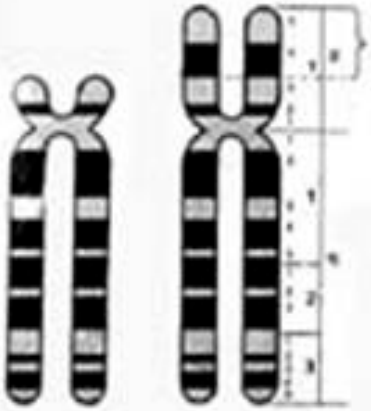
Low muscle tone (hypotension) and clinodactyly.

Moderate facial abnormalities: vertical folds of the skin covering the inner corners of the eyes, wide-set eyes (hypertelorism) and a small circle of the head.

The diagnosis can be confirmed only by chromosome analysis.

Cats Syndrome





Lejeune's syndrome

Deletion of the short arm of the 5th chromosome the genes CTNND2, SEMA5A and TERT

The CTNND2 gene (OMIM: 604275) encodes delta-catenin, a protein that plays a crucial role in the nervous system (isolated autism defect)

The SEMA5A gene (OMIM: 609297) encodes the semaphorin proteins involved in the signaling processes of axonal targeting. They have a predominantly repulsive effect on the cone of axon growth, rejecting it from germination into unsuitable regions

The TERT gene (OMIM +187270) encodes the telomerase reverse transcriptase (TERT) telomerase reverse transcriptase (TERT), which is part of the telomerase enzyme, which adds repeating DNA sequences (TTAGGG) to the 3 'end of the DNA strand in the telomere region located at the ends of all human chromosomes.

Crying is like a cat's cry,
Anomalies of the larynx,
Children grow poorly,
Lag behind in mental development,
Microcephaly,
A person with hypertelorism,
Micrognathia,
Epicanth,
Ears are wrong, low set

The cause of such crying are the following defects of the laryngeal cartilage:
decreased epiglottis;
narrowing of the respiratory tract in the epiglottis;
softening of cartilaginous tissue;
folds on the mucous membrane lining the cartilage of the larynx.

There are 4 main signs of Lesian syndrome from the side of the eye:

An antimonyholoid section of the eyes.

Strabismus.

Eye hypertelorism.

Epicant.

Manifestations of catnip screaming in childhood:

mental retardation;
decreased muscular tone;
violation of coordination of movements;
constipation;
moonlike face;
short neck;
lability of behavior;
problems with eyesight.

There are several types of mutations in which this disease develops:

Complete lack of a short shoulder. In the total absence of a short shoulder, about a quarter of the genetic information encoded by the fifth chromosome is lost. This is the most frequent and most severe variant of the disease. In addition to the genes that cause the development of Lejeune's syndrome, several important parts of the molecule are lost. This predisposes to more serious and numerous innate anomalies.

Shortening of short arm. With the shortening of the shoulder, only part of the genetic information that was closer to the end of the molecule (from one-third to one-half of the shoulder) is lost. If the deletion of the site 5p12.2 - 5p12.3 takes place, on which the key genes are located, then the child develops a cat scream syndrome. In such cases, there are fewer developmental defects than in the absence of the entire shoulder (less genetic information is lost).

Formation of the ring chromosome. The so-called ring chromosome is a clutch of the two shoulders of the same chromosome (long and short). As a result, the molecule takes the form of a ring. This anomaly involves the deletion of a small terminal site. If the key genes are lost, the disease develops.

Mosaic form of the syndrome.

The mosaic form of the syndrome is usually the easiest option, but is extremely rare. In all three previous cases, the child received a defective DNA molecule from one of the parents. In a mosaic form, the genome was originally normal. The so-called zygote (the cell obtained at the confluence of the spermatozoon and the ovum) had full-fledged fifth chromosomes. The problem occurred during the growth of the embryo. When dividing the chromosomes, the short arm was lost (not divided between two daughter cells). Thus, a part of the cells (usually a large part) will have a normal genome in the future, and a small part - a genome, characteristic of Lesian syndrome. The severity of the pathology will be moderate in this case, and the children will have fewer developmental defects (the defects of some cells are partly compensated by the enhanced division of others). Such children are not normal in the full sense of the word. As a rule, mental retardation still takes place. However, deviations in physical development and severe congenital malformations of internal organs are usually not observed.

Diagnosis of cat litter syndrome :?

anamnesis collection;

karyotyping of parents;

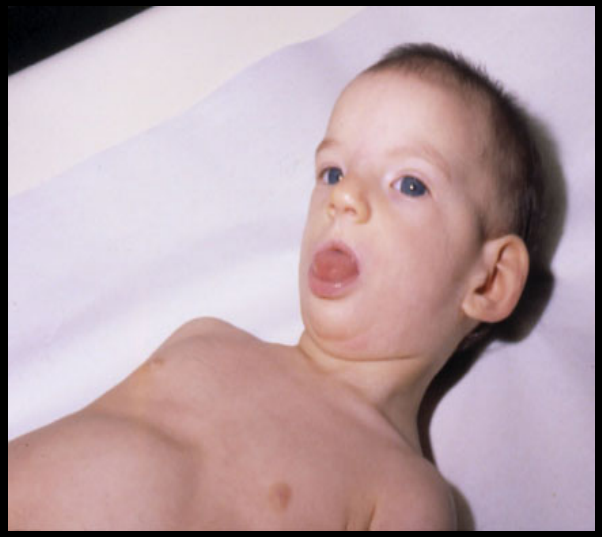
ultrasonography;

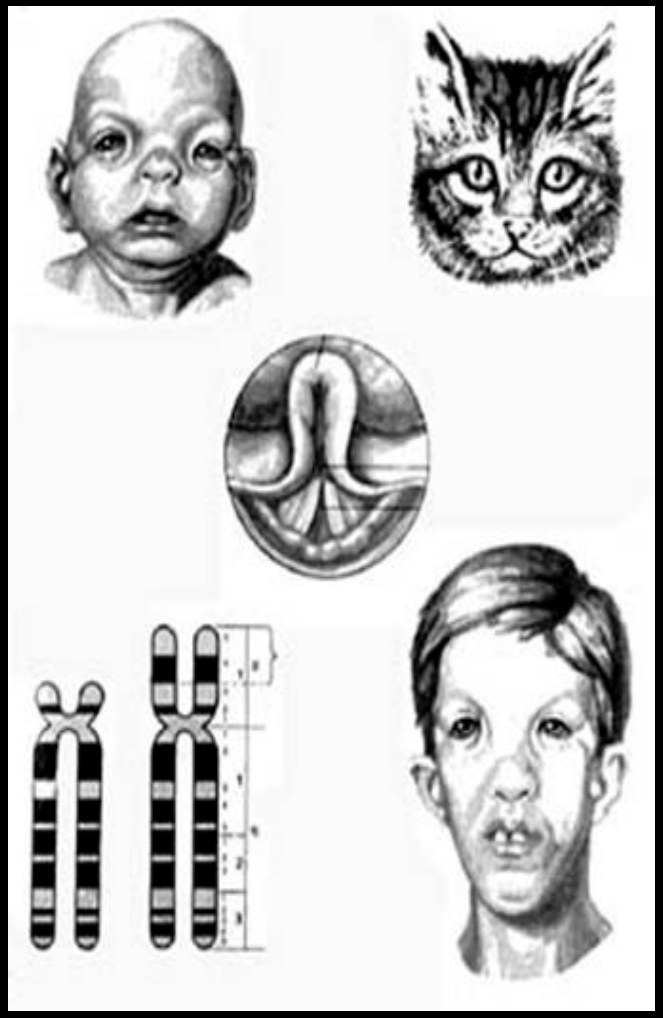
blood test for plasma markers;

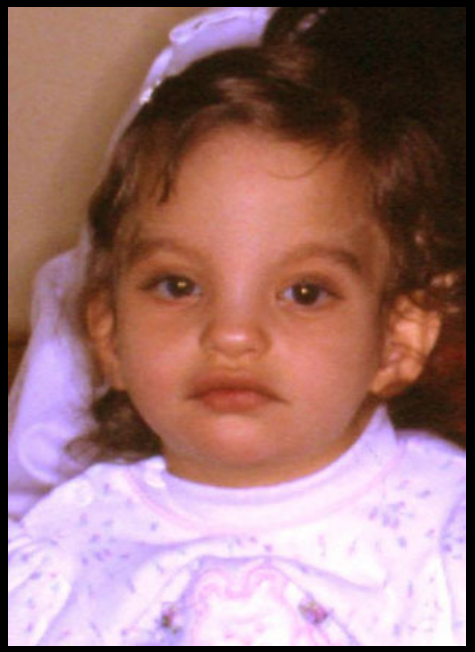
invasive research;

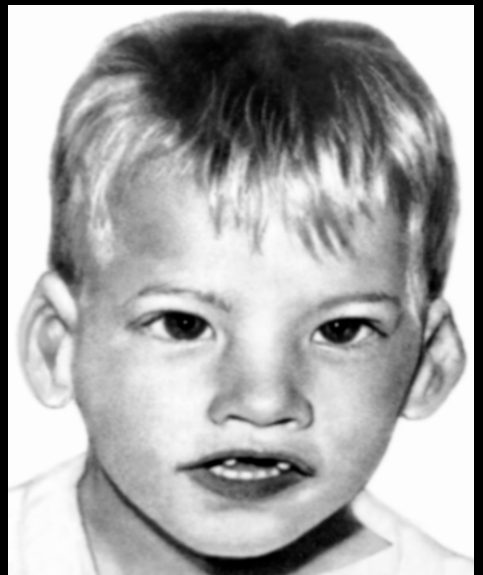
diagnosis at the postpartum stage.

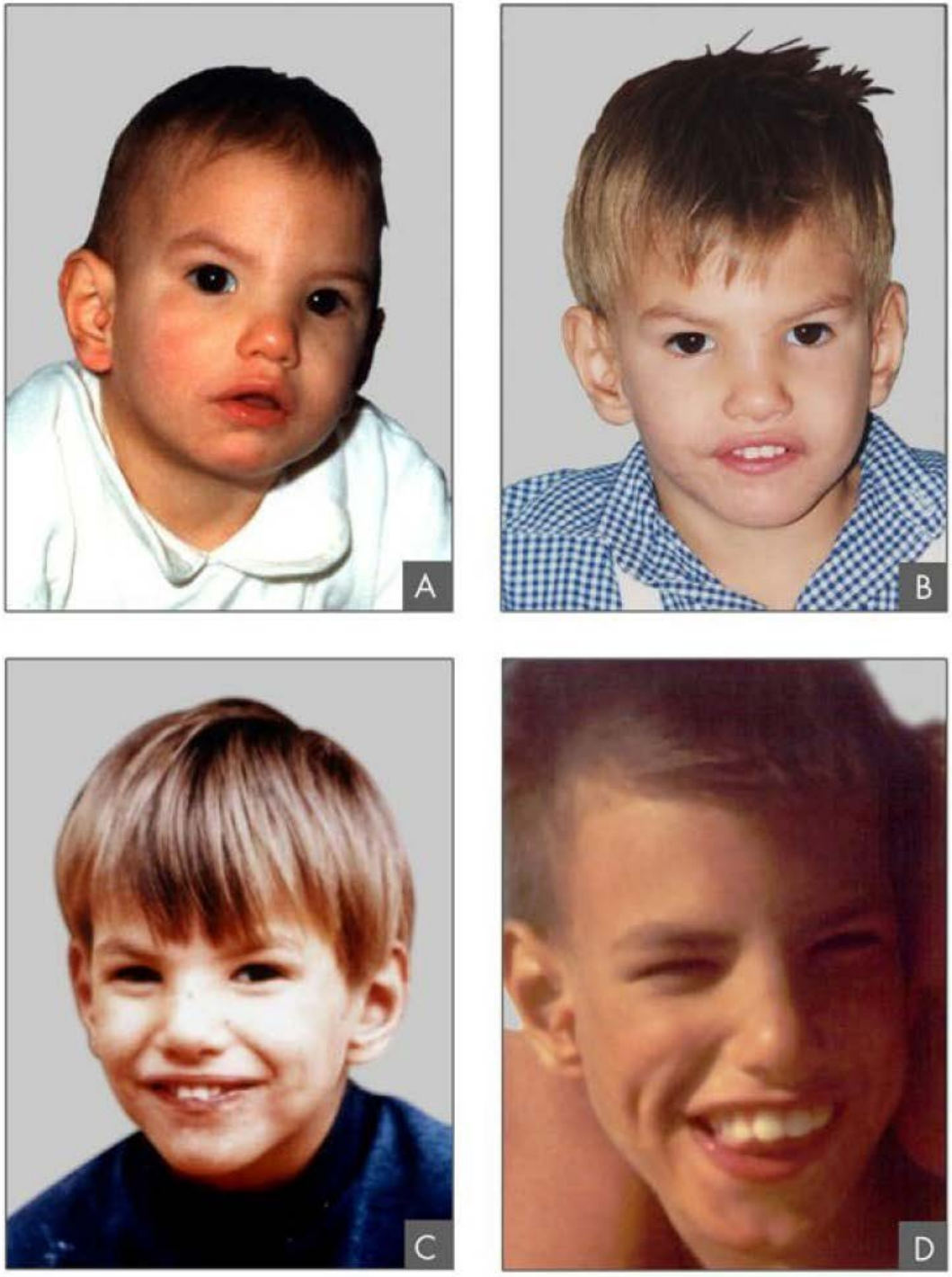
Appearance of the patient with the syndrome of "cat's scream":










A
B
C
D