Down Syndrome (Trisomy 21) — Causes, Symptoms and Diagnosis

Down Syndrome, or trisomy 21, is not only the most common chromosomal aberration, but also the most frequent genetic cause of mental retardation. Nowadays, it is possible to assess the risk of having a child with Down syndrome via cytogenetic examination and to discuss the matter in detail with the respective families. Learn more about the epidemiology, clinical picture and diagnostics of Down syndrome and discover its most important treatment options.

Definition

Down syndrome as a mental and physical handicap
Trisomia 21, also known as Down syndrome, is a chromosomal aberration that leads to the presence of 3 copies of chromosome 21.

In trisomy 21, patients show delayed or miscarried mental and physical development. The syndrome is named after the English physician J. Langdon Down who first described the disease in 1866.

Epidemiology

Down syndrome in the population
With a prevalence of 1 in 700, trisomy 21 is the most common autosomal chromosome aberration. It is also the most frequent genetic cause of mental retardation in humans. Life expectancy in those with this condition is currently around 50 years and tends to increase due to improved therapeutic options.

The older the mother, the higher is the risk of Down syndrome. The risk of Down syndrome in children born to women below 30 years is less than 1 in 1000. In 40 to 44-year-old mothers, 10–20 in 1000 children are affected, and for mothers over 44 years, 20–40 in 1000 children are affected with Down syndrome.

Note: The older the mother, the higher the risk of trisomy 21!

Etiology

Causes of Down syndrome

The underlying cause of the condition is a trisomy — a triple set of chromosomes. In Down syndrome, there is an extra chromosome 21, resulting in 3 instead of 2 chromosomes. On a cytogenetic level, the following possibilities could lead to the development of trisomy 21:

Free trisomy 21: in >90% of all cases; the surplus chromosome 21 is free, caused by non-separation and is usually of maternal origin (dependent on the age of the mother; chromosome number: 47).
Trisomy 21 due to translocation: in approx. 2–4% of all cases, the surplus chromosome 21 is attached to another acrocentric chromosome (often 14) (Robertsonian translocation). The age of the mother does not have any influence here (chromosome number: 46).

Trisomy 21 in mosaic: In 1–2% of all cases, there is the simultaneous existence of a normal cell line and another with trisomy; the phenotype depends on the distribution pattern in the brain.

Partial trisomy 21: Very rare, duplication of one segment of chromosome 21.

Trisomy 21 due to translocation occurs de novo (by mutation) or is inherited. Here it is possible that the parents are carriers of a balanced translocation with a well-balanced
genotype and without any clinical symptoms. If the father is a carrier of the translocation, the empirical risk of recurrence (likelihood for an ill child) is approx. 1–2%. If the mother carries it, the risk increases to 10–15%. With a translocation to chromosome 14, the maternal karyotype would look like this: 46, XX, t(14;21).

If there is a 21/21 translocation, the risk of trisomy 21 is 100%.

Clinical Picture

Symptoms of Down syndrome

While there is no difference between the symptoms of a free trisomy and those of a trisomy due to translocation, the degree of manifestation of a mosaic trisomy depends on the number of cells with trisomy.

The affected show increased susceptibility to infections and a more frequent occurrence of leukemia.

Phenotype of Down syndrome

Patients with Down syndrome have a characteristic outer appearance with the following dysmorphic features that can occasionally be found in the normal population:

Craniofacial: brachycephaly, flattened and broad nasal bridge, oblique lid axis in the
superior and lateral direction, epicanthus, small mouth and chin, macroglossia, furrows in the lips and tongue, high roof of the mouth, abnormal teeth, abnormal auricles, Brushfield spots (whitish concentration of the iris), cataract, strabismus, nuchal fold, and short neck.

**Image:** "Feet of a 10-year-old boy with Down Syndrome, with the typical large space between the large toe and second toe." by Loranchet. License: CC BY 3.0

**Acral:** shortened and broad hands and feet, clinodactyly, brachydactyly, single transverse palmar crease, and separation of the 1st and 2nd toes (sandal gap).

**Musculoskeletal system:** hypotension of the muscles, hypermobility of joints, umbilical/inguinal hernia, diastasis recti, surplus ribs, abnormal vertebral bodies, leveled angle of the acetabulum and ilium, and stunted growth.

**Skin:** rough, dry, mottled

**Note:** the mentioned abnormalities can also be found in the normal population and are hence not specific for Down syndrome!

**Organic malformations in Down syndrome**

**Image:** "Cryptorchidism, undescended testis" by Nevit Dilmen. License: CC BY-SA 3.0

In addition to changes in the exterior, **organs** can also be malformed. Patients with Down syndrome can suffer from **hypothyroidism**. Furthermore, males, unlike females, are mostly **infertile** and exhibit **cryptorchidism**.

However, the most common (up to 50%) malformations are **congenital heart diseases**. They include, mostly, an **atrioventricular septal defect**, in addition to other heart diseases like a **ventricular septal defect**, a **patent ductus arteriosus Botalli**, or
isolated atrial septal defects.

Concerning the intestinal tract, duodenal atresia and Hirschsprung’s disease are common. Other possibilities include atresia of the esophagus or anus as well as malformation of the bile duct and pancreas.

Mental retardation in Down syndrome

The IQ of patients with trisomy 21 lies between 20 and 50. The mental retardation can, however, vary considerably in its severity. Usually, it is possible to learn how to read and write so that in some cases, the possibility of an autonomous life exists.

Diagnosis

Postnatal diagnosis of Down syndrome

The diagnosis of trisomy 21 can often be suspected postnally based on the clinical picture. Since many symptoms of Down syndrome can also be found in the normal population, Jackson et al. (1976) created an index to contribute to the visual diagnosis. The index lists the following 25 symptoms of Down syndrome:

1. Brachycephaly
2. Oblique lid axis in the superior and lateral direction
3. Nystagmus
4. Flattened nasal bridge
5. Narrow roof of the mouth
6. Cynodactyly of the 5th finger
7. Hypotension of the muscles
8. Sandal’s gap
9. Folded auricle
10. Short neck
11. Epicanthus
12. Blepharitis, conjunctivitis
13. Brushfield spots
14. Constantly open mouth
15. Abnormal teeth
16. Protruding tongue
17. Scrotal tongue
18. High roof of the mouth
19. Nuchal fold
20. Shortened and broad hands
21. Brachydactyly of the 5th finger
22. Single transverse palmar crease
23. Congenital heart diseases
24. Cardiac murmur
25. Hyperflexible ligaments

If at least 13 of these symptoms are noticed in a child, the child has a 100% probability of trisomy 21. The occurrence of 10-12 characteristics indicates a probability of 85%; 7-9 characteristics indicate a 75% chance of the condition, and 5-6, a likelihood of 23%. If less than 5 characteristics can be found, the probability is 0%.
It is, however, necessary to confirm the diagnosis via cytogenetic examinations (analysis of the karyotype) in order to diagnose or rule out Down syndrome. It is also important to determine the underlying type of trisomy 21 in order to be, among other things, able to assess the risk of recurrence (see above).

Prenatal diagnosis of Down syndrome

**Triple test**

The **triple test** is used between the 16th and 20th weeks of pregnancy. The triple test measures the **blood serum levels** of the mother and compares them to **reference values** of other pregnant women in the same week of pregnancy. The test includes **β-hCG**, **α-fetoprotein**, and **estriol**. If those values differ from the standard (**β-hCG** high, **α-fetoprotein**, and estriol low), trisomy 21 can be the reason. This test is, however, **not specific** for Down syndrome and susceptible to faults. It is also necessary to calculate the exact gestational age in order to be able to draw a conclusive comparison.

**Sonography**

![Image: Atrioventricular septal defect. Four-chamber view shows the absent crux (arrow). RA – right atrium, LA – left atrium, RV – right ventricle, LV – left ventricle. By: openi. License: CC BY 2.0](image)

Sonography could be used to detect **malformations** like a flat face, macroglossia, shortened femur, lack of ossification of the nasal bone, shortened fingers, dilated renal pelvis, or heart defects. These malformations increase the risk of trisomy 21 but cannot always be interpreted as a manifestation of a disease. Sonography can thus yield **false-positive** or **false-negative** results.

Sonography of **fetal nuchal translucency** (subcutaneous tissue between the neck and cervical spine) in the 11–14th week of pregnancy is also indicative of Down syndrome. However, this finding is also **not specific** for trisomy 21.

![Image: Ultrasound image of measurements of fetal nuchal translucency, and absent nasal bone at 11 weeks of pregnancy. CVS demonstrated a trisomy 21 of the fetus. By: Wolfgang Moroder. License: CC BY-SA 3.0](image)

**Amniocentesis and chorionic villus sampling**
If non-invasive examinations like sonography or the triple test show noticeable findings, invasive examinations like amniocentesis and chorionic villus sampling need to be considered. For this procedure, the fetal or placental cellular material is extracted and chromosomal analysis is performed. Both methods can diagnose a trisomy 21 with a high degree of certainty; they are, however, known to be associated with an increased risk of miscarriage.

**Treatment of Down Syndrome**

Organic malformations have to be treated symptomatically. For example, hypothyroidism can be treated by substituting thyroxine; congenital heart diseases can be operated in order to considerably increase the quality of life. Physiotherapy (as early as possible) can mitigate the extent of muscular hypotension.

It is also essential to encourage the affected children and to treat them with all the care they need. Hence, they need a loving environment as well as medical and psychosocial care. Caring for a child with Down syndrome is often a special challenge for the parents, so it can be helpful for them to join self-help groups. The accessibility of a social pediatric center is also useful.

Medical check-ups are important for patients with trisomy 21. It is crucial to watch out for abnormalities of the gastrointestinal tract and heart in newborn babies and infants. It is also necessary to detect eye diseases like cataract and strabismus as early as possible in order to prevent additional handicaps due to visual impairment.

**References**


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