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

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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 of Down Syndrome

Down syndrome as a mental and physical handicap
Trisomy 21, also known as Down syndrome, is a chromosomal aberration that leads to a triple presence of chromosome 21.

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

Epidemiology of Down Syndrome

Down syndrome in the population
A prevalence of 1:700 makes trisomy 21 the most common autosomal chromosome aberration. It is also the most frequent genetic cause of mental retardation in humans. Life expectancy 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: if the mother is below 30 years, less than one child in 1000 is born with trisomy 21; in the group of 40- to 44-year-old mothers, 10 to 20 of 1000 children are affected, and mothers over 44 years give birth to 20 to 40 of 1000 children with Down syndrome.

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

Etiology of Down Syndrome

Causes of Down syndrome

As the name of the disease suggests, the underlying cause is a trisomy, thus a triple set of chromosomes. Chromosome number 21 is in surplus and exists thrice rather than twice. On a cytogenetic level the following possibilities are conceivable for the development of trisomy 21:

Free trisomy 21: in > 90% of all cases; the surplus chromosome 21 is free, caused by non-separation and usually of maternal origin (dependent on the age of the mother); chromosome number: 47.
Trisomy 21 due to translocation: in approx. 2 to 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 to 2 % of all cases, 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 to 2%. If the mother carries it, the risk amounts raise to 10 to 15%. With a translocation to chromosome 14, her karyotype would look like this: 46, XX, t(14;21).

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

Clinical Picture of Down Syndrome

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 amount of cells with trisomy.

The affected show increased susceptibility for 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 sometimes also be found in the normal population:
Craniofacial: brachycephalie, flattened and broad nasal bridge, oblique lid axis towards superior and lateral, epicanthus, small mouth and chin, macroglossia, furrows in lips and tongue, high roof of the mouth, abnormal teeth, abnormal auricles, Brushfield spots (whitish concentration of the iris), cataract, strabismus, nuchal fold, 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.”
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Acral: Shortened and broad hands and feet, clinodactyly, brachydactyly, single transverse palmar crease, separation of first and second 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, 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.
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Not only the outer appearance of the patients is different, but organs can also be malformed, too. Patients with Down syndrome can, for example, suffer from hypothyroidism. Furthermore, male patients are, contrarily to the female ones, mostly infertile and exhibit cryptorchidism.

The most common (up to 50%) malformations are, however, represented by congenital
heart diseases. They include, above all, an atrioventricular septal defect but also other heart diseases like a ventricular septal defect, a patent ductus arteriosus Botalli or isolated atrial septal defects.

Concerning the intestinal tract, you can often find duodenal atresia or Hirschsprung’s disease. You may also possibly find atresia of the esophagus or anus as well as malformation of the bile duct and the 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 of Down Syndrome

Postnatal diagnosis of Down syndrome

The diagnosis of trisomy 21 can often be suspected postnatally on the basis of 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 towards superior and lateral
3. Nystagmus
4. Flattened nasal bridge
5. Narrow roof of the mouth
6. Clynodaktyly V
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. Brachydaktyly V
22. Single transverse palmar crease
23. Congenital heart diseases
24. Cardiac murmur
25. Hyperflexible ligaments

If at least 13 of these symptoms can be noticed in a child, the child suffers from trisomy 21 with a probability of 100%. 12 to 10 characteristics mean a probability of 85%; 9 to 7 one of 75% and 6 to 5 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, moreover, 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 the 20th week of pregnancy. It 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), a 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**

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

Sonography of the **fetal nuchal translucency** (subcutaneous tissue between neck and cervical spine) in the 11th to 14th week of pregnancy can also lead to the suspicion of increased risk of Down syndrome. Still, this examination is also **not specific** for trisomy 21.
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 with it. 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, furthermore, 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 often presents 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 useful, too.

Medical check-ups are also quite important for patients with trisomy 21. It is indispensable to watch out for abnormalities of the gastrointestinal tract and of the heart in newborn babies or later in 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.

Review Questions

You can find the correct answers beneath the list of references.

1. A woman at the age of 35 gives birth to a child with Down syndrome. Which symptom is the child least likely to exhibit?
   - A. Brushfield spots
   - B. Abnormalities of the auricle
   - C. Single transverse palmar crease
   - D. Cleft palate
   - E. Macroglossia

2. A couple comes to you in your human genetic consultation. They have one child with trisomy 21 and want to know the risk of recurrence for their second child. The cytogenetic examination of the father shows that he is a carrier of a balanced translocation (46, XY, t(14;21)). How likely is it for the couple to give birth to another child with Down syndrome?
   - A. 1 %
   - B. 5 %
   - C. 10 %
   - D. 15 %
   - E. 20 %
3. Which diagnostic method delivers the safest diagnosis of trisomy 21?

A. Triple test  
B. Sonography  
C. Chorionic villus sampling  
D. Double test  
E. Auscultation

References


**Correct answers**: 1D, 2A, 3C

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