Review: Down's syndrome- causes and clinical manifestation

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ABSTRACT

One of the most frequent disorders, Down syndrome (DS), has enormous social and medical consequences. A variety of features have been linked to DS, including congenital heart abnormalities, leukemia, Alzeihmer's illness, and Hirschsprung disease. Affected to differing degrees by various qualities are people with DS. Determining the cause of this diversity is thus a significant issue for about 1 in 800 infants. It is related to abnormalities in several physiological systems, some of which might cause serious and fatal issues. The important factors to take into account when visiting kids with Down syndrome and the clinical problems associated with the condition will be covered in this article.

Keywords: Down syndrome, DS, Trisomy , Tri+21

Introduction

Trisomy 21 is the genetic disorder that causes Down syndrome. Down syndrome (DS) is the most common chromosomal abnormality, affecting one in every 800 babies (1). A third copy of chromosome 21—whole or partial—causes it (47 chromosomes). Millions of people have learning and memory issues, congenital heart disease (CHD), Alzheimer's disease (AD), leukemia, cancer, and Hirschprung disease (HD) due to DS, a leading cause of intellectual disability (2-6). John Langdon Down, an English physician, developed the initial idea behind Down's syndrome in the late nineteenth century; as a result of his discovery, he earned the moniker "Father of this Disease" and the sickness was named in his honor. Jerome, a French doctor, discovered that people with Down syndrome now had 47 chromosomes, up from 46 in 1959. When the chromosomal origin of the illness was identified more than 90 years later (7-8), the condition was named Down syndrome (9).

Individuals with Down syndrome are capable of development and socialization, and early intervention is frequently employed with affected children and their families. Health treatment and other forms of assistance are difficult to get. Intellectual impairment is generally mild, and phenotypic variance among individuals is substantial. The social function, which might range from weak to severe, is often good compared to cognitive impairment. There are significant variances in the occurrence and presentation of DS based on ethnicity and geographic area. Scientists found 329 genes that cause Down's syndrome in 21 chromosomes in 2000. (10). Recent advances in medical therapy and societal support have enhanced the DS population's life expectancy. People with Down syndrome typically have a 55-year lifespan in high-income countries (11)

Down Syndrome Types

There are three types of DS:

A) Non-disjunction Down's syndrome: Trisomy 21 is the most prevalent type of Down syndrome. Before the egg and sperm join, the mistake starts in either the sperm or the egg, where there is an extra chromosome. About 95% of cases contain trisomy 21. Trisomy 21 is caused by non-disjunction, which is more common in older cells and is of maternal origin in roughly 88% of instances. This explains why older women give birth to children who have Trisomy 21 (12-14).

B) Mosaic Down's syndrome: The mistake in cell division happens after conception and affects 1-2% of persons with DS. Affected people have a mix of 47 and 46 chromosomes, with one extra chromosome in the 47 groups. Mosaic DS is not hereditary, and it is thought that 1-2% of those with DS have it. There are two cell lines within the Mosaic Down individual: one Trisomy 21 and one normal. Individuals have different proportions of cell lines. Due to non-disjunction or an anaphase lag, mosaicism occurs after conception (a temporary delay in the cell cycle). Trisomic-21 zygotes produce certain Mosaic Down syndrome patients, but normal zygotes produce other Mosaic Down syndrome patients. Because parental chromosomal analysis is not required, genetic counseling should be the same for a kid with normal Trisomy Down syndrome. Mosaic Down syndrome patients may outperform other forms of Down syndrome kids on Intelligence testing and have fewer medical issues (10,11).

C) Translocation: It happens when a fragment of an extra copy of chromosome 21 transfers to another chromosome during cell division in an egg or sperm cell. This happens before fertilization. People with this condition have three copies of chromosome 21, two of which are normal and one extra copy attached. Because sperm or eggs from persons with balanced translocation have a significant chance of producing an abnormal kid, the person, in this case, will be clinically normal but risk producing chromosomally imbalanced translocation. Around 4% of DS patients experience translocation, which can be Robertsonian or reciprocal. Reciprocal translocations, the most frequent form, include chromosomal exchanges between types, such as 1 and 9 (10,11).

When chromosomal material is switched back and forth between two non-homologous chromosomes, a translocation takes place. Both parents of a child diagnosed with Translocation Down syndrome should be tested for chromosomal abnormalities to assess the likelihood of a second case. Non-disjunction trisomy 21 is not a risk factor for the development of translocation Down syndrome. When both parents carry one copy of the translocation, the likelihood of conceiving a child with translocation Down syndrome increases by around 12% and 1.2% for each parent, respectively, after a live delivery.

Several clinical diseases linked to Down syndrome:

Some of the diseases and conditions linked to DS include Alzheimer's, heart disease, leukaemia, high blood pressure, and digestive disorders.

Complication of DS

1) **development**

Early development is typically delayed in children with Down syndrome. Intellectual disability ranges from moderate to severe in children with Down syndrome. Problems with both receptive and expressive language are more severe than those caused by other disorders. Working memory deficits are also more pronounced (15).

2) **neurological**

Seizures affect 5%–6% of DS children, with 40% of these people exhibiting symptoms in infancy (16). The most common types of seizures are infantile spasms and tonic-clonic seizures with myoclonus (17). Compared to other causes of infantile spasms, children with Down syndrome had a more favorable outcome and therapeutic response. In DS patients, the probability of dementia increasing after age 50 rises to 70% (18). The progress of Alzheimer's disease at a young age has been connected to several genes. Several genes are mentioned in this paper, including APOE (apolipoprotein E), APP (amyloid precursor protein), BACE2 (beta-secretase 2), PICALM (phosphatidylinositol-binding clathrin assembly protein), and PICALM (Apolipoprotein E). Dementia in Down syndrome individuals is commonly attributed to

a trisomy of amyloid precursor protein (APP), a crucial membrane protein in brain synapses.

3) **cardiac**

Congenital heart disease (CHD) is most frequently associated with DS, which affects about 50% of children (19). Most often seen congenital heart problems are atrioventricular septal defects, atrial septal abnormalities, and tetralogy of Fallot. All high-risk babies with DS should consult a cardiologist and have echocardiography within 6 weeks (20). Airway and respiratory abnormalities in Down syndrome can cause pulmonary hypertension and right-sided problems (21). It's possible that mitral valve prolapse and aortic regurgitation might occur in older children. If you want to catch heart issues early, DSMIG suggests doing an annual cardiac auscultation.

4) **Hearing**

Almost 50% of individuals with Down syndrome have sensorineural and/or conductive hearing loss (22). Conduction hearing loss is most frequently caused by otitis media with effusion. Between 6 and 10 months after birth, all neonates should get a thorough audiological assessment. This should be followed by a monthly screening program.

5) Gastrointestinal problems

In about 2% of Down syndrome kids, Hirschsprung disease is present. DST and IA are both 260 and 33 times more likely to happen than DS (23,24). Myenteric ganglion cell deficiency in a colon segment causes HD, a low intestinal obstruction (25). Losing ganglion cells in children with HD prevents the distal intestine from relaxing properly. Due to the absence of peristaltic waves passing through the aganglionic segment and the absence of regular defecation, there is a functional blockage. The most common symptoms within days of birth are abdominal distention, meconium inability, enterocolitis, and bilious vomiting.

Bilious vomiting is a symptom of early neonatal duodenal atresia or DST in infants. Common causes of gastro-oesophageal reflux include a decrease in lower oesophageal tone and a delay in sitting up straight. If your child has a persistent cough and recurrent pneumonia, think about aspiration pneumonia (26).

6) **Visual**

Down syndrome is associated with refractive problems, squints, accommodation disorders, nystagmus, congenital cataracts, and newborn glaucoma (22). Each evaluation should check for squinting, gaze abnormalities, visual behavior, and attention, especially in younger children. If anomalies are apparent earlier, they should be referred to an orthoptist and ophthalmologist or optometrist for a comprehensive ocular/visual evaluation at 27 months. 9 One-third of children will be diagnosed with an ocular/visual abnormality at this stage due to the frequency of vision problems (22).

Other medical complications related to Down

Other important medical concerns that affect people with Down syndrome at a higher rate than the general population are:

Leukemia ;

In a 1962 research of 2033 patients with Down's syndrome under 20, leukemia was shown to have an 18-fold greater fatality rate compared to the general population of England and Wales (23). More recent research that linked the National Registry of Childhood Tumours with the National Down Syndrome Cytogenetic Record found that 1.7% of the 766 Down's syndrome children born after 1989 had leukemia, 43 times the risk for the general population of 0.04%. 22 Hayes and coworkers found that leukemia affected 1.65% of Dublin children (24).

The two types of leukemia that affect persons with Down syndrome most frequently are acute lymphatic and acute non-lymphatic (25). Most acute nonlymphatic leukemia is acute megakaryoblastic leukemia, which occurs in children under four. This kind of leukemia is uncommon in young children in the general population. Transient megakaryoblastic lukaemia affects 10% of Down's syndrome babies. 25% of babies with this illness will develop acute megakaryoblastic lukaemia between one and four years (26).

Thyroid Disease;

A review of much research on hypothyroidism related to Down's syndrome revealed an overall frequency of around 3% in children and about 11% in adults (28). Newborn screening detects

0.7% of Down syndrome newborns with chronic primary congenital hypothyroidism, many times greater than the overall population (27). Another research conducted in 1991–1992 on 55 Down's syndrome kids aged 5 to 16 who attended special schools in Oxfordshire reported that 12.7% of the kids had hypothyroidism that needed to be treated (95% confidence interval, 3.9 to 21.5). When the thyroid function of 160 persons with Down syndrome was evaluated, it was shown that 35% of them had thyroid malfunction (hypothyroidism in 8%, subclinical hypothyroidism in 24%, and hyperthyroidism in 3%) (29).

Epilepsy;

Epilepsy affects around 0.8% of the general population (30). A Belfast research discovered that 9% of 191 individuals (aged 18 and over) with Down's syndrome developed epilepsy. As advancing years, the frequency rose, reaching 46% in people over 50. According to another research, 201 individuals with Down's syndrome comprised 16% who had epilepsy, with the majority (66%) getting it at 16 or older. In both studies, clinical signs of dementia were linked to late-onset epilepsy.

Alzheimer's disease ;

In 1987, a gene on chromosome 21 was discovered that codes for an amyloid precursor protein, a protein thought to be involved in the development of Alzheimer's disease. Down's syndrome and Alzheimer's disease have long been known to be related (31). The study of Down syndrome with Alzheimer's disease continues. The majority of Down syndrome patients who die beyond the age of 30 have brain disorders such as Alzheimer's (32). In a five-to-ten-year study of 307 adults with Down syndrome who lived in institutions, the number with dementia grew from 11% between 40 and 49 to 77% between 60 and 69 (33). Dementia affects everyone over 70 and starts at 56 years old. Age-related frequency and onset have been documented elsewhere. 32 Dementia, including Alzheimer's disease, is 2% in 65-70-year-olds and 10% in 85-year-olds (32).

General principles;

► Most of the time, a pediatrician specializing in Down syndrome should take care of a child with Down syndrome (a community pediatrician, neuro-disability specialist, or general pediatrician).

► After their first year, children should be assessed annually.

► Children with Down syndrome require a multi-disciplinary neurodevelopmental team that includes a paediatric cardiologist, a speech therapist, and a physical therapist.

► Infants and children with Down syndrome need to be checked for heart, hearing, vision, thyroid, growth, development, and sleep-disordered breathing issues.

► A clearly defined individual should take up care coordination throughout the transition, generally a General Practitioner (34).

Genetics and recurrence risk

A triple quantity of the chromosomal region leads to the Down syndrome phenotype. This is generally caused by an extra chromosome 21 in all cells, which is why it is frequently referred to as Trisomy 21. 21q22.2-q22.3 (35). Translocation Down syndrome and Mosaic Down syndrome are two less prevalent types. All newborns with Down syndrome should have chromosomal analysis to discover a translocation or mosaic genotype, which may affect recurrence in later pregnancies and prognosis (36).

The DS complex phenotype is caused by a variation in gene dosage on human chromosome 21. (Hsa 21). Recent years have been a concerted attempt by scientists to fully characterize Hsa 21 because of its essential role in DS and its modest size. 21q is 33.5 Mb in size, but 21p is only 5-15 Mb (37). When the original sequence of 21q was revealed, a total of 225 genes were estimated. Hsa 21 contains 40.06% repetition content, with SINEs, LINEs, and LTRs having 10.84%, 15.15%, and 9.21% repeat content, respectively.

The most prevalent cause of DS is trisomy, which is caused by an extra copy of chromosome 21. Some potential possibilities include Robertsonian translocation and isochromosome ring abnormalities. During egg sperm maturation, two long chromosomal arms detach simultaneously, forming an isochromosome. Chromosome 21 fails to separate during egg or sperm development,

resulting in trisomy 21 (karyotype 47, XX, + 21 for females and 47, XY, + 21 for males). Robertsonian translocations, in which chromosome 21's long arm is connected to another, account for just 2%-4% of all chromosomal translocations (generally chromosome 14). Mosaicism involves cell division errors after fertilization. Thus, mosaic DS patients have two tissue and organ cell lineages (one with 21 chromosomes and one with the normal number).

When two copies of chromosome 21 refuse to separate during the paternal germ cell development process, an extra copy is usually the result. In scientific terms, this is called a non-disjunction. Trisomy 21 results from a maternal non-disjunction 88% of the time, a paternal non-disjunction 9% of the time, and a mitotic non-disjunction 3% of the time. Non-disjunction in the first meiotic division in the female embryo is responsible for 75% of maternally derived trisomy 21, and recent data suggests that it may originate in this division (38).

Trisomy 21;

Standard Trisomy 21 accounts for around 95% of cases of Down syndrome. Non-disjunction (failure to separate chromosomal homologs) during meiosis I or meiosis II causes this to happen. It is still unknown what causes non-disjunction and its link to advancing maternal age. Because trisomy 21 is rarely inherited via families, chromosomal analysis in either parent is unnecessary. The recurrent probability of Down syndrome in women under 30 is 0.5%. However, the risk of recurrence appears to be the same or slightly higher for women over 30.

Prenatal Diagnosis ;

Prenatal detection of Down syndrome has evolved with cell-free prenatal screening and parallel sequencing of maternal plasma cell-free DNA (cfDNA) (39). The parent who is a translocation carrier and the pregnant woman at increased risk of bearing an affected offspring can benefit from cfDNA's high specificity (99.7%) for the diagnosis of DS. At the time of the prenatal diagnosis of DS, parents should be informed about the possibility of evaluating the fetus for possibly curable cardiac and gastrointestinal problems. If prenatal ultrasonography identifies a congenital abnormality, the parents are more likely to seek diagnostic testing (cfDNA).

A diagnosis of DS can only be made when genetic testing of an amniocentesis or chorionic villus sample reveals the karyotype. This 99% accurate study may assist parents in deciding whether to continue the pregnancy or get prenatal diagnostics. Patients of any age who are pregnant or may become pregnant are encouraged by the American College of Obstetricians and Gynecologists to carefully consider all of their options when it comes to prenatal screening and diagnostic tests (40). Clinicians should recognize that informing parents of a suspected DS diagnosis before or during delivery has a major impact. Compassionately, quickly, privately, and with supportive family or friends, the information must be conveyed. Parents want congrats first.

Advancement in the diagnosis

The paralogous sequence quantification (PSQ) method measures the Has 21 copy number utilizing paralogous sequences. PSQ is a PCR-based approach that uses paralogous genes to identify specific chromosomal number abnormalities. Despite having a high degree of sequence similarity, paralogous sequences undergo nucleotide alterations in a locus-specific manner. Pyrosequencing can quantify paralogous sequence mismatches (PSMs) to determine chromosomal dosage. Diagnostic laboratories may use PSQ to diagnose common aneuploidies in 48 hours. Pyrosequencing quantifies sequencing (41). Finally, Complete trisomy or monosomy, as well as partial (segmental), aneuploidies, can be determined by comparative genomic hybridization (CGH) with BAC chips (42,43).

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