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Down Syndrome

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ABSTRACT: Trisomy 21, another name for Down syndrome, is a genetic disorder brought on by an extra copy of chromosome 21. About 1 in 700 live births worldwide have this chromosomal abnormality, making it one of the most prevalent. The condition is characterized by a combination of physical features, developmental delays, and varying degrees of intellectual disability.

A single deep furrow across the hand, upward-slanting eyes, and a flat facial profile are typical physical characteristics. A number of illnesses, such as thyroid disorders, respiratory and hearing issues, and congenital heart defects, are also more likely to affect people with Down syndrome. The quality of life and life expectancy of people with Down syndrome have been greatly enhanced by early intervention programs, inclusive education, and regular medical treatment. To improve outcomes for impacted people and their families, encourage inclusion, and strengthen support, more research and advocacy are needed.

KEYWORDS: Down Syndrome, chromosomal abnormality, thyroid disorder.

I. INTRODUCTION

Autosomes, sex chromosomes, or both may be affected by a numerical change in one or more chromosomes, resulting in Down syndrome (DS), a genetic condition. that has been the focus of multidisciplinary research and displays a range of physical and medical characteristics, a unique look, and a learning impairment The genesis, clinical manifestations, cognitive and behavioral traits, medical consequences, and societal viewpoints related to Down syndrome are all thoroughly reviewed in this article.

In order to provide a more knowledgeable and encouraging environment for people with Down syndrome, this review attempts to provide a useful resource for special educators, healthcare professionals, legislators, and the general public by compiling the body of available knowledge. (1-2) Depending on maternal age and prenatal screening protocols, 1 in 400–1500 newborns born in various populations have Down syndrome (DS), the most common chromosomal defect in humans. (3) Mental retardation, congenital heart defects, gastrointestinal abnormalities, weak neuromuscular tone, dysmorphic head, neck, and airway features, visual and auditory impairment, distinctive facial and physical features, hematopoietic disorders, and an increased risk of other illnesses are all associated with it. As the mother ages, the likelihood of having children with Down syndrome rises

However, because younger women have higher fertility rates, the likelihood of having a child with Down syndrome rises with the mother's age, and over 80% of DS infants are born to women under 35. (4–7).

II. HISTORICAL BACKGROUND

In 500 Alzheimer's patients, Martinez-Frias discovered the syndrome, which is characterized by pronounced trisomy 21 facial traits. The disease can be observed clearly in paintings from the 15th and 16th centuries, according to various scientists. Potteries were the earliest factual evidence of trisomy 21 around 2500 years ago, when Bernal and Briceno believed that some of the sculptures depicted people with the condition. In 1838, Esquirol defined the phenotypic features of trisomy 21. Children having common characteristics that set them apart from other children with mental impairment were described by English physician John Langdon Down. Since these kids appeared to be from Mongolia, he called them "Mongoloids." (8–11)

Although the etiology of Down syndrome was unclear until the middle of the 20th century, the disorder was named after John Langdon Down, a physician who identified it for the first time in 1866. It had been proposed by Waardenburg and Davenport in 1932 that trisomy 21 might be caused by a chromosomal defect. (8, 12, 13)

III. PATHOPHYSIOLOGY

The other possible root causes of trisomy 21 are a zygotic or ring chromosome and Robertsonian translocation. Another chromosome, primarily chromosome 14, is joined to the long arm of chromosome 21. Two distinct cell lines result from the mistake of division following fertilization in mosaicism. In Robertsonian translocation, an isochromosome occurs when two long arms split together rather than the long and short arms. Between 2% and 4% of patients experience this. Down syndrome is linked to an additional copy of chromosome 21 because it prevents chromosome 21 from separating during gametogenesis, leaving an extra copy in every cell of the body. (14)

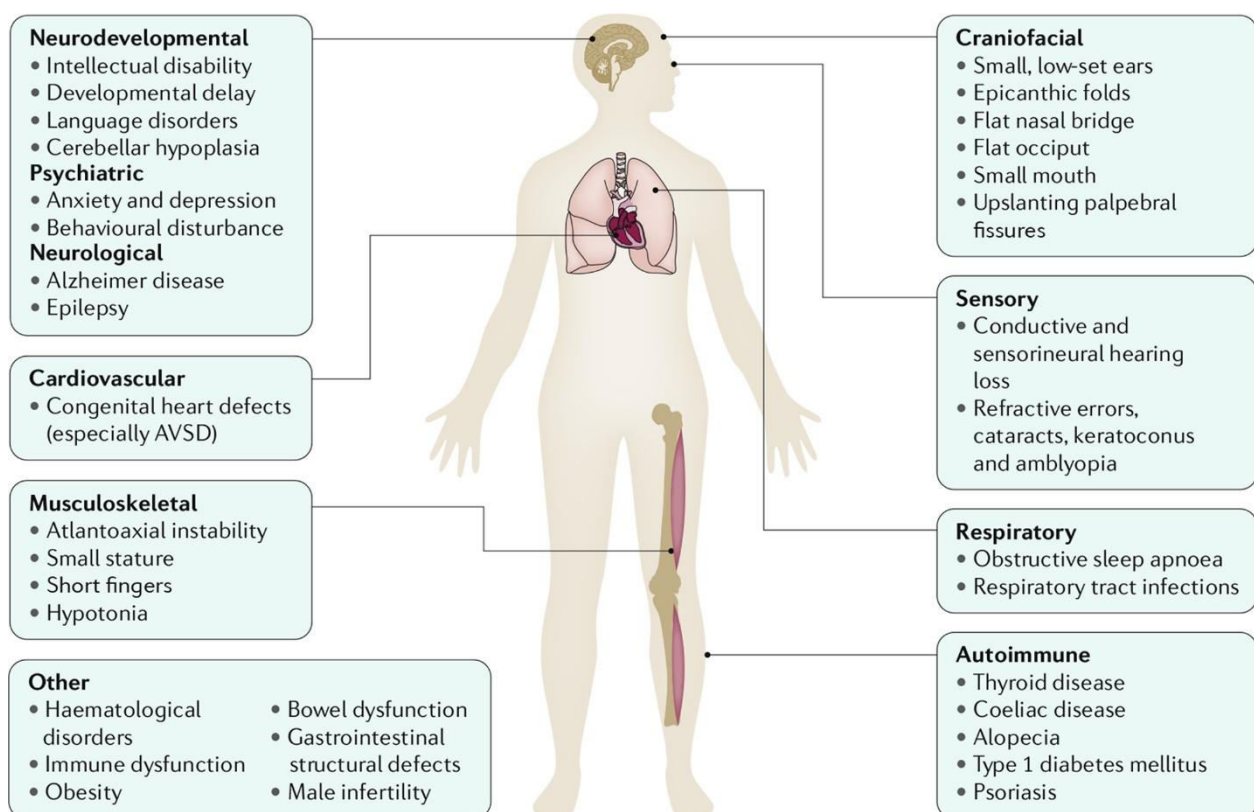
Genetics of the disease

Trisomy caused by an extra copy of chromosome 21 is the most frequent cause of DS children. Other reasons include isochromosomal or ring chromosomes and Robertsonian translocation. When two long chromosomal arms split together during the formation of an egg or sperm, instead of the long and short arms splitting together, this condition is referred to as an isochromosome. The inability of chromosome 21 to split during the formation of an egg or sperm results in trisomy 21 (karyotype 47, XX, + 21 for females and 47, XY, + 21 for males). The long arm of chromosome 21 is joined to another chromosome (usually chromosome 14) in Robertsonian translocation, which happens infrequently in 2-4% of cases. On the other hand, mosaicism addresses the mistake or misdivision that happens during cell division after fertilization. As a result, persons with mosaic DS have two cell lineages—one with the typical number of chromosomes and the other with a further number of 21—that contribute to their tissues and organs. (15)

Clinical features

Since Down syndrome affects various systems, it is linked to a range of clinical disorders. These patients exhibit a wide range of symptoms, including neurological or intellectual and developmental difficulties, congenital heart issues, gastrointestinal (GI) abnormalities, and distinctive facial traits. (16)

Prevalence



The As the world's population increases, the lifetime prevalence of DS is rising significantly. For instance, according to unpublished data, the population prevalence of DS in the USA rose from almost 50,000 in 1950 (3.3 per 10,000 people) to almost 212,000 in 2013 (6.7 per 10,000 people) (17).

Symptoms and Manifestations in Down syndrome

Although there is individual diversity, people with trisomy 21 (the presence of a supernumerary chromosome 21; often known as Down syndrome (DS)) exhibit a unique set of symptoms and manifestations that impact many body systems. Short stature, short fingers, hypotonia, and atlantoaxial instability are common characteristics of people with DS. Epicanthic folds, a flat nasal bridge and occiput, a tiny mouth and ears, and upward-slanting palpebral fissures are all features of the face. Heart abnormalities that are congenital are prevalent, especially.

lack of the atrioventricular septum (AVSD). A number of health conditions, such as hypothyroidism, obstructive sleep apnea, epilepsy, hearing and vision problems haematological disorders (including leukaemia), recurrent infections, anxiety disorders, and early-onset Alzheimer disease, are also more common in people with DS than in the general population. (18)

IV. ETIOLOGY

An additional copy of chromosome 21 is present in most Down syndrome patients. The genetic origin of Down syndrome and the relationship between various genotypes and phenotypes are the subject of several theories. One of these is gene dosage imbalance, where a higher dosage or quantity of Hsa21 genes leads to a greater growth of the gene. It also covers the potential link between various genes and distinct Down syndrome manifestations. The other well-known theory is the amplified development instability hypothesis, which holds that a stronger influence on the expression and regulation of numerous genes is caused by the genetic imbalance caused by several trisomic genes. (19)

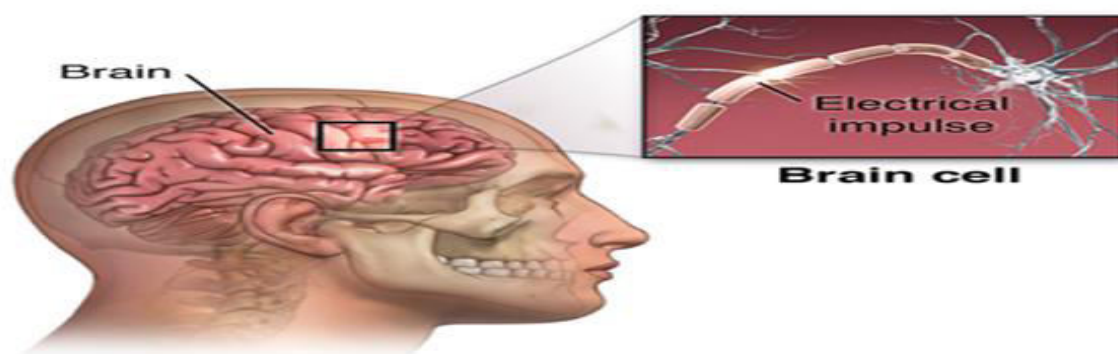
Disorders and Disease Associated with Down Syndrome

Neurological disorder

Trisomy of Has 21 has been linked to decreased brain volume, particularly in the cerebellum and hippocampal regions. Almost all babies with Down syndrome have hypotonia, which is their defining characteristic. It is the cause of these patients' delayed motor development and is characterized by less resistance to passive muscle strain. [20]

(a) Epilepsy (a) Alzheimer illness

Epilepsy disease Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures. These seizures, which range from momentary loss of consciousness to convulsions, are brought on by aberrant electrical activity in the brain. a condition where seizures are brought on by abnormalities in the brain's nerve cell activity. A hereditary condition or an acquired brain injury can cause epilepsy.



Hematological Disorders

A distinct range of cancers, including solid tumors and leukemias, are seen in patients with DS. Leukemia in DS patients was first reported in 1930 [21], and the first comprehensive investigation was conducted in 1957 [22]. They make up around 10% of pediatric acute myeloid leukemia (AML) and 2% of all pediatric acute lymphoblastic leukemia (ALL). Somatic mutations impacting the GATA 1 gene (also known as GATA-binding factor 1) are linked to the leukemogenesis of acute megakaryoblastic leukemia (AMKL) in people with Down syndrome [23]. A transcription

factor connected to chromosome X, GATA 1 is necessary for the differentiation of erythroid and megakaryocytic cells. These GATA 1 mutations result in the synthesis of a shorter GATA 1 protein, which causes immature megakaryocytes to proliferate uncontrollably.[24,25]

A transitory myeloproliferative disease, which is characterized by the presence of blast cells in infants with Down syndrome younger than three months, is another condition that is highly specific to the condition. It is identified in the first week of life and goes away by three months. It is typified by the clonal proliferation of megakaryocytes. About 10% of patients with Down syndrome are known to have it, which is sometimes referred to as transitory aberrant myelopoiesis or transient leukemia. Abortion may occur spontaneously if something happens to the fetus. (26, 27)

Gastrointestinal Disorders

The distal intestine cannot relax normally in HD children due to the lack of ganglion cells. Functional obstruction results from the absence of regular defecation and the failure of peristalsis waves to pass through the aganglionic segment. The main symptoms, which start to show up a few days after birth, are bilious vomiting, enterocolitis, abdominal distention, and failure to pass meconium. Early in the neonatal era, infants with duodenal atresia or DST exhibit bilious vomiting. Severe electrolyte imbalance and dehydration will ensue if treatment is not received.

Anal atresia, cardiovascular anomalies, tracheoesophageal fistula, esophageal atresia, renal, and limb defects are all linked to an increased incidence of IA, a birth defect in which the rectum is malformed. These conditions are collectively referred to as the VACTERL association. (28)

This disease has been associated with changes in about ten non-Hsa21 genes. In addition to the structural abnormalities, individuals with Down syndrome are at risk for a number of additional gastrointestinal conditions, such as celiac disease, persistent constipation, GERD, and intermittent diarrhea. It is advised to perform yearly celiac disease screening because there is a strong correlation between celiac disease and Down syndrome, which is present in around 5 percent of these patients. These people will need to follow a gluten-free diet for the remainder of their lives after receiving a diagnosis. (29)

Musculoskeletal Disorders

vitamin D shortage brought on by a number of things, such as insufficient exposure to Among other things, these patients had accelerated breakdown due to anticonvulsant medication, malabsorption from celiac disease, UV exposure, and insufficient vitamin D consumption. These variables make children with Down syndrome more susceptible to frequent fractures and raise their risk of decreasing bone mass. (30) Due to hypotonia and greater ligamentous laxity, which results in gross motor delay, children with Down syndrome are more likely to have decreased muscle mass. abilities and may cause a dislocated joint. (31)

Diagnostic methods

The most widely used invasive prenatal diagnostic procedure worldwide is amniocentesis. From 15 weeks onward, amniocenteses are typically done to obtain amniotic fluid for karyotyping. Early amniocentesis is defined as amniocentesis carried out prior to 15 weeks of pregnancy. CVS, which involves aspiration or biopsy of the placental villi, is often carried out between 11 and 13 (13+6) weeks of gestation. Despite being very dependable, amniocentesis and CVS raise the risk of miscarriage by 0.5 to 1% when compared to the background risk (32–34).

Risk factor

Non-disjunction of homologous chromosomes or chromatids during the meiotic divisions that take place during egg development is linked to this risk. (35) Furthermore, for these kinds of maternal errors, distinct altered recombination patterns have been found, only a portion of which are linked to maternal age. (36) Maternal MI or MII mistakes were used to stratify these results. The study's findings highlight how risk factors vary depending on the kind of error. For instance, some polymorphisms in candidate genes that code for synaptonemal complex components (like SYCE2) were linked to meiosis I faults, whereas others (like SYCP2) were linked to MII problems.

Numerous genes are involved in meiotic processes like recombination. Therefore, there is a compelling reason to examine whether human meiotic nondisjunction is predisposed to by genetic variations. An untargeted genome-wide association study (GWAS) of HSA21 nondisjunction in mothers who gave birth to a child with trisomy 21 resulting from a maternal mistake was carried out utilizing the mothers as cases and the fathers as controls. The study included a candidate gene analysis. (37)

These positions involved exposure to solvents in the workplace, according to an initial review. These kinds of studies are required to investigate the association between maternal and paternal HSA21 nondisjunction and particular exposures to hazardous substances in the home and workplace. The discovery that exposure to endocrine-disrupting substances alters meiosis and raises the incidence of aneuploidy highlights this. For instance, both sexes' reproductive systems—including the ovaries, testes, and reproductive tract—are impacted by exposure to the common environmental pollutant bisphenol A (BPA) and other endocrine-disrupting substances (38–40).

Treatment / Managements

- Although feeding issues improve following heart surgery, a balanced diet, consistent exercise, and physical therapy are necessary for optimal growth and weight gain.
- Parental education is one of the most crucial aspects of managing Down syndrome since parents need to be aware of the different conditions that may be associated with it in order to
- Other specialties involved include a developmental pediatrician, pediatric pulmonologist, gastroenterologist, neurologist, neurosurgeon, orthopedic specialist, child psychiatrist, physical and occupational therapist, speech and language therapist, and audiologist.
- These individuals need to have their vision and hearing evaluated, and prompt surgery is necessary because they are more likely to develop cataracts. Annual thyroid function tests should be performed, and any abnormalities should be treated appropriately.
- Regardless of the clinical manifestations of congenital heart illness, cardiac referrals need to be made for every patient. If this is present, it should be fixed within the first six months of the child's life to guarantee the best possible growth and development.
- Patients with Down syndrome are managed by a multidisciplinary team. Karyotyping should be performed on newborns suspected of having Down syndrome in order to confirm the diagnosis. For both parents' genetic testing and counseling, the family must be sent to a clinical geneticist. (41)

Differential Diagnosis

- Congenital hypothyroidism
- Mosaic trisomy 21 syndrome
- Partial trisomy 21(or 21q duplication)
- Robertsonian trisomy 21
- Trisomy 18
- Zellweger syndrome or other peroxisomal disorders

Treatment

DS has no known medical cure. Nonetheless, early medical assistance and the start of developmental therapies in childhood might be beneficial for kids with DS. Physical treatment, occupational therapy, and speech therapy may be beneficial for children with Down syndrome. They might get help in school and special education. In the last few decades, there has been a noticeable improvement in the life expectancy of individuals with DS (42-44).

Researchers have recently used this transcriptional silencing paradigm to address the issue of extra gene expression in DS. The researchers employed zinc-finger nucleases to introduce the inducible X inactive specific transcript (non-protein-encoding) (XIST) into chromosome 21 of induced pluripotent stem (iPS) cells obtained from a patient with DS. The Xist transgene's mechanism of transcriptional silencing seems to entail coating chromosome 21 with Xist RNA, which causes heterochromatin to be permanently modified. After the newly inserted transgene was induced in the iPS cells, XIST noncoding RNA was expressed, coating chromosome 21 and causing chromosome inactivation (45).

The mammalian dosage compensation system known as X inactivation makes sure that every cell in both male and female animals has a single active X chromosome (Xa) for a diploid pair of autosomes. In female cells, this is accomplished by silencing one of the two X chromosomes. Xist non-coding RNA is responsible for the silencing of the X chromosome and is linked to chromatin modification (46).

V. CONCLUSION

A common genetic disease called Down syndrome is brought on by an additional copy of chromosome 21 (trisomy 21). Developmental delays, distinctive physical characteristics, and an elevated risk of specific medical disorders are

the results. Despite the fact that there is no cure, people with Down syndrome can greatly enhance their quality of life via supportive therapies, medical care, special education, and early diagnosis. Many people with Down syndrome can lead healthy, happy, and productive lives if they get assistance from their families and are included in society. To improve our knowledge of the relationship between phenotype and genotype, a number of ideas have been proposed. To improve our knowledge of the relationship between genotype and phenotype, a number of ideas have been proposed. Trisomy 21, or DS, is the most prevalent chromosomal anomaly in live births and is linked to several congenital abnormalities. Since DS is linked to a number of clinical disorders, managing these patients calls for a coordinated multidisciplinary strategy and ongoing patient monitoring, both of which have been covered in this review paper.

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