Down Syndrome: A Narrative Review

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Abstract

Down syndrome is the most frequent chromosomal disorder in people and the most widely recognized chromosomal disorder in terms of intellectual impairment. The main cause of the syndrome is trisomy of chromosome 21, which results in several systemic problems. Individuals may have varying degrees of symptoms and often experience developmental delays and an intellectual disability that lasts a lifetime. However, there is a large range of phenotypic variation; not all problems manifest in every case. The condition cannot be managed or cured with medication or surgery. Therefore, the focus of treatment is on the range of health issues, medical conditions, and intellectual, developmental, and physical challenges that individuals with Down syndrome may face throughout their lives rather than the disorder itself. Physical therapy, early intervention, assistive technology, prescription drugs, and even surgery are all possible options. This narrative review aims to provide an overview of Down syndrome, its genetic basis, clinical manifestations and current management approaches.

1. Introduction

In 1866 John Langdon Down, an English physician, first described the condition in a seminal paper titled "Observations on the Ethnic Classification of Individuals with Intellectual Disabilities". He proposed a theory suggesting the classification of various conditions based on ethnic characteristics. This included the well-known "Mongolian type" of individuals suffering from what would later be named Down syndrome. [1] However, it was not until almost a century later in Paris that Dr. Jerome Lejeune linked Down syndrome to chromosome 21 making it the first instance in global history where an intellectual disability was connected to a chromosomal abnormality. This revelation not only paved the way for extensive research in modern genetics but also gave rise to a new scientific discipline: cytogenetics. [2]

Down syndrome is the most prevalent chromosomal anomaly in humans and is caused by the presence of all or part of the third copy of chromosome 21. Furthermore, trisomy 21, which produces this disease, is the most common live-born aneuploidy. [3]

2. Epidemiology

The occurrence of Down syndrome escalates with advancing maternal age and varies among different populations, ranging from 1 in 319 to 1 in 1000 live births [4] Additionally, it is recognized that the frequency of Down syndrome in foetuses is relatively high at the time of conception. However, a significant proportion, approximately 50% to 75%, of these foetuses are lost before reaching full term. [5]

Other autosomal trisomies are more common than Trisomy 21, but their postnatal survival rates are significantly inferior when contrasted with Down syndrome. The higher survival rate in individuals with Trisomy 21 is ascribed to the presence of a restricted number of genes on chromosome 21, referred to as Hsa21, which stands out as the smallest and least densely populated among the autosomes. [6]

3. Etiology and Genetic Variation/ Pathophysiology

Most individuals diagnosed with Down syndrome exhibit an additional chromosome 21 stemming from the failure of proper segregation of chromosome 21 during gametogenesis, leading to an extra chromosome in all cells of the body. Two alternative causes of trisomy 21 include Robertsonian translocation and isochromosome or ring chromosome. Isochromosome occurs when both long arms separate together instead of the long and short arm, while Robertsonian translocation, occurring in 2% to 4% of patients, entails the attachment of the long arm of chromosome 21 to another chromosome, typically chromosome 14. Mosaicism, conversely, involves two distinct cell lines due to an error in division following fertilization.[4]

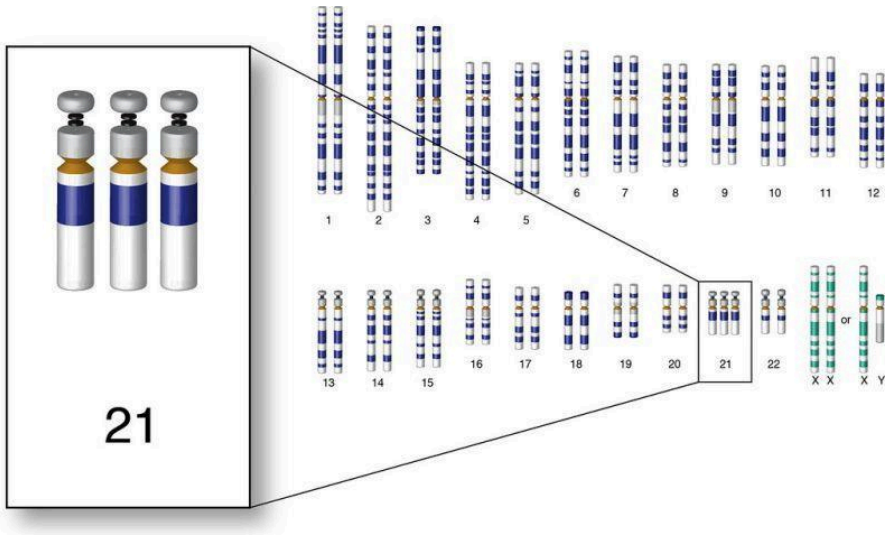

Fig.1 Pictoral presentation of Triosomy of chromosome 21 resulting in Down Syndrome [10]

Various hypotheses explore the genetic underpinnings of Down syndrome and the correlation between different genotypes and phenotypes. One such hypothesis involves gene dosage imbalance, where an elevated dosage or quantity of Hsa21 genes leads to increased gene expansion. An alternative well-accepted hypothesis is the amplified developmental instability theory, suggesting that the genetic imbalance resulting from multiple trisomic genes has a more significant impact on the expression and regulation of a multitude of genes. [7]

4. Signs and Symptoms/ Clinical Features

Individuals with Down syndrome often encounter difficulties in memory and learning, stemming from the neotenization process affecting both the brain and body, guiding them toward a state reminiscent of fetal development including slowed maturation, incomplete morphogenesis, and the occurrence of atavisms.[8]
Prevalent clinical features that are primary manifestation and almost guaranteed indications of DS entail changes in craniofacial characteristics such as

- Oblique eye fissures accompanied by epicanthic skin folds on the inner corner of the eyes
- A "flat and broad" face
- Brushfield spots (white spots on the iris of eyes)

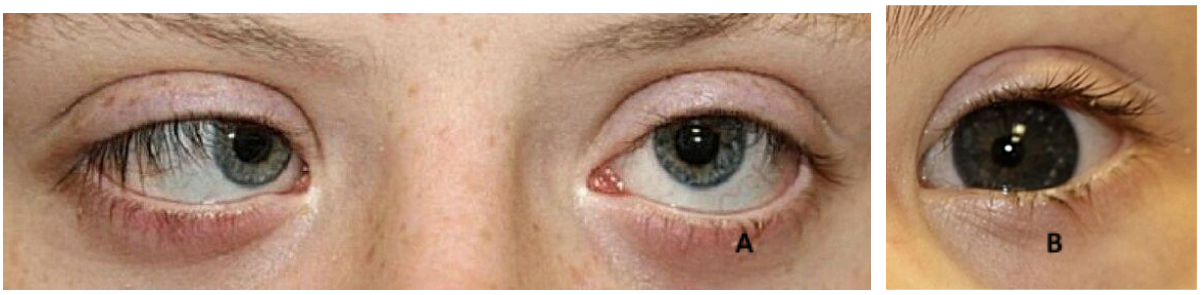

Fig.1 A. Clinical photograph of oblique eye fissures accompanied by epicanthic skin folds on the inner corner of the eye. B. Clinical photograph demonstrating "Brushfield spots" in a patient with Down syndrome [9]

Other symptoms include excessive joint laxity, increased space between the large toe and second toe, a single flexion furrow of the fifth finger, and short fingers. Muscle hypotonia, a flat nasal bridge, a single palmar fold, a protruding tongue (resulting from a small oral cavity and an enlarged tongue near the tonsils, known as macroglossia), a short neck, microgenia (an abnormally small chin), and muscle hypotonia. Less common manifestations of DS may involve congenital heart malformations, leukemia, or gastrointestinal abnormalities. However, the severity of these defects can vary. [8]

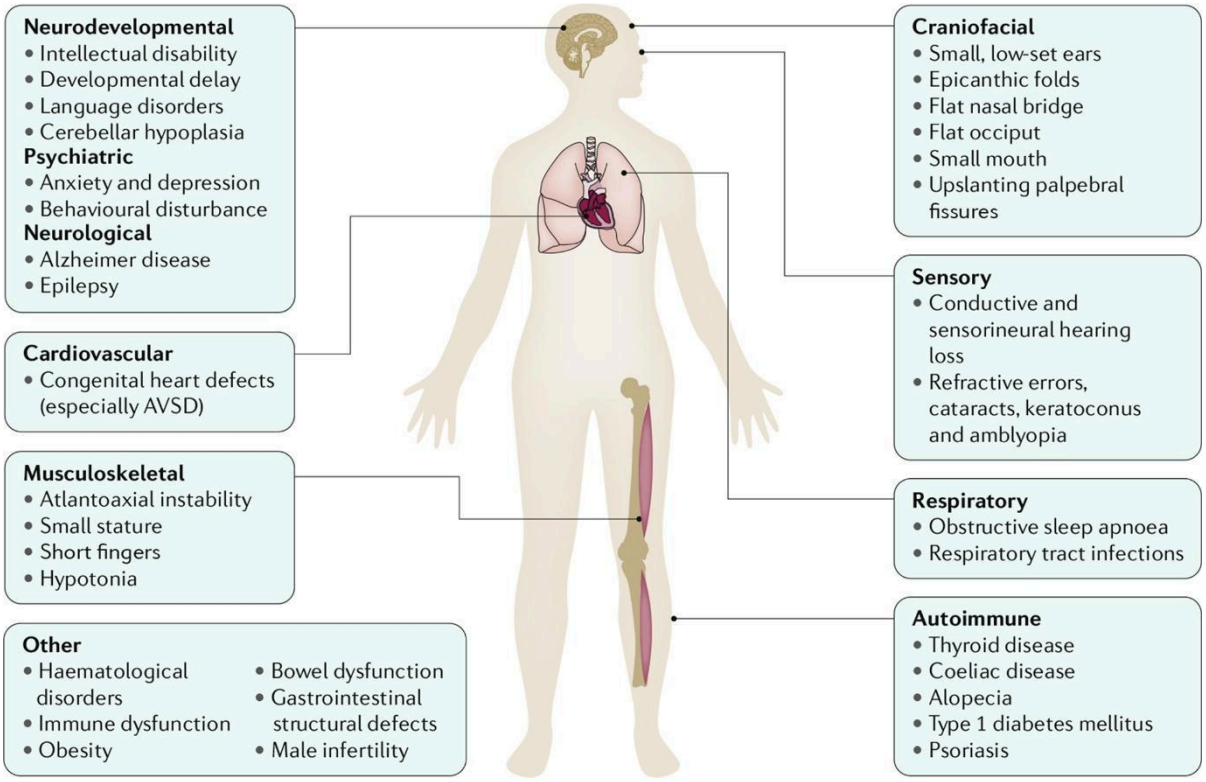

Fig.2 Pictorial presentation of Symptoms and manifestations in Down syndrome.[10]

5. Diagnosis by Rapid Detection of Trisomy 21

Various techniques are utilized to perform prenatal screenings for Down syndrome. The use of ultrasound between the 14th and 24th weeks of gestation serves as a diagnostic tool, relying on soft markers such as heightened nuchal fold thickness, the absence or reduction of the nasal bone, and enlarged ventricles. [11]

If the foetus is deemed to be at risk of Down syndrome due to the manifestation of the mentioned symptoms, the foetus may undergo further screening for DS, which entails extracting a sample of genetic material. Once extracted, the sample undergoes examination for additional material from chromosome 21, potentially indicating the presence of Down syndrome. [12,13] The following tests can then be conducted to detect trisomy 21:

Amniocentesis:
Amniocentesis involves the extraction of a sample of amniotic fluid, subsequently subjected to chromosomal analysis for the identification of additional genetic material. This diagnostic procedure is restricted to the gestational period between weeks 14 and 18.[12]

Chorionic villus sampling (CVS):
CVS entails the procurement of a cell sample from a specific region of the placenta to assess the presence of an extra chromosome. This investigative technique is conducted within the time frame of weeks 9 to 11 of pregnancy. [13]

While the above tests are widely employed for diagnosis, there exists a minimal risk of miscarriage ranging from 0.5% to 1% due to their invasive nature. [13] Several alternative

techniques have been created and are utilized for the swift detection of trisomy 21, both in foetal development and postnatal. The predominant method entails Fluorescence In Situ Hybridization (FISH) directed at interphase nuclei, employing either Hsa21-specific probes or the entire Hsa21. [14,15]

Additional non-invasive prenatal diagnostic techniques are under investigation for prenatal Down syndrome diagnosis. These methods rely on detecting fetal cells in maternal blood and the presence of cell-free fetal DNA in maternal serum. [15] Other methods that are being studied for the detection of trisomy 21 include digital PCR and next-generation sequencing (NGS). [16]

6. Treatment and Management

Caring for individuals with Down syndrome necessitates a comprehensive multidisciplinary approach. One crucial aspect of this is the education of the patient's parents. It is crucial for parents to gain an understanding of the diverse potential conditions associated with Down syndrome, enabling them to pursue timely and appropriate diagnoses and treatments. Treatment for Down syndrome primarily focuses on addressing symptoms and achieving complete recovery is generally not feasible, however, various management methods can be adopted.[17]

Management of down syndrome is done in 4 major phases:

- Early Intervention and Educational Therapy- Encompassing a variety of specialized initiatives and support systems, professionals offer tailored programs to support very young children with Down syndrome and their families. These experts may consist of special educators, speech therapists, occupational therapists, physical therapists, and social workers. [18]
- Treatment Therapies
- Drugs and Supplements – Some individuals with Down syndrome may choose to use amino acid supplements or medications affecting brain activity. However, several recent clinical trials investigating these treatments lacked proper control and revealed adverse effects. Subsequently, more targeted psychoactive drugs have been developed. Nevertheless, there is a shortage of controlled clinical studies confirming the safety and efficacy of these medications for Down syndrome. [19]
  Studies on drugs targeting dementia symptoms in Down syndrome have frequently had a small number of participants. The results of these studies have not definitively proven the benefits of these drugs.[20]
- Assistive Devices – Supportive strategies for children with Down syndrome incorporate the utilization of assistive devices, encompassing a diverse range of materials, equipment, tools, or technologies intended to enhance learning and simplify task execution. Instances include amplification devices designed to tackle hearing issues, bands aiding movement, specialized pencils for improved writing, touchscreen computers, and computers featuring keyboards with larger letters.[21]

Summary

An interprofessional team is essential to manage patients with Down syndrome. Karyotyping should be performed on newborns suspected of having Down syndrome in order to confirm the diagnosis. The family should be referred to a clinical geneticist so that both parents can receive genetic testing and counseling. The child needs to see an ophthalmologist, orthopaedic surgeon, cardiologist, dermatologist, gastroenterologist, physical therapist, mental health nurse, ENT surgeon, and behavior specialist because nearly every organ system is affected. One of the most significant aspects of managing Down syndrome is educating parents about the various conditions that may be linked to it. This will help parents get their child diagnosed and treated properly. The course of treatment is essentially symptomatic, and full recovery is not achievable. For both adults and children with Down syndrome, a better understanding of the disorder and early interventions can significantly improve their quality of life and enable them to lead satisfying lives.

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