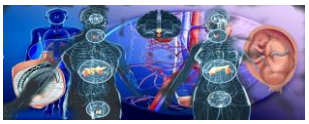
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Down Syndrome: An Outcomes of Developmental Disorders

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Abstract

Down syndrome (DS) is a birth defect with huge medical and social costs, caused by trisomy of whole or part of chromosome 21. It is the most prevalent genetic disease worldwide and the common genetic cause of intellectual disabilities appearing in about 1 in 400-1500 newborns. Although the syndrome had been described thousands of years before, it was named after John Langdon Down who described its clinical description in 1866. Scientists have identified candidate genes that are involved in the formation of specific DS features. These advances in turn may help to develop targeted therapy for persons with trisomy 21.

Keywords: Ultrasonography; noninvasive prenatal screening; aneuploidy; chromosome abnormality

Introduction

Down syndrome (DS) is the most frequently occurring chromosomal abnormality in humans and affecting between 1 in 400-1500 babies born in different populations, depending on maternal age, and prenatal screening schedules . DS is the common genetic cause of intellectual disabilities worldwide and large numbers of patients throughout the world encounter various additional health issues, including heart defects, hematopoietic disorders and early-onset Alzheimer disease. The syndrome is due to trisomy of the whole or part of chromosome 21 in all or some cells of the body and the subsequent increase in expression due to gene dosage of the trisomic genes . It is coupled with mental retardation, congenital heart defects, gastrointestinal anomalies, weak neuromuscular tone, dysmorphic features of the head, neck and airways, audiovestibular and visual impairment, characteristic facial and physical features, hematopoietic disorders and a higher incidence of other medical disorders.

Etiology

Approximately 2500 years ago, Bernal and Briceno thought that certain sculptures represented individuals with trisomy 21, making these potteries the first empirical indication for the existence of the disease Martinez-Frias identified the syndrome in 500 patients with Alzheimer disease in which the facial features of trisomy 21 are clearly displayed. Different scientists described evident illustration of the syndrome in 15th and 16th century paintings. Esquirol wrote phenotypic description of trisomy 21 in 1838.

Genetic basis

Chromosome 21 is the smallest human autosome with 48 million nucleotides and depicts almost 1–1.5% of the human genome. The length of 21q is 33.5 Mb and 21 p is 5–15 Mb. More than 400 genes are estimated to be on chromosome 21. Chromosome 21 has 40.06% repeat content comprising short interspersed repeatitive elements (SINEs), long interspersed repeatitive elements (LINEs), and long terminal repeats (LTRs).

Pathophysiology

An extra copy of chromosome 21 is associated with Down syndrome, which occurs due to the failure of chromosome 21 to separate during gametogenesis resulting in an extra chromosome in all the body cells. Robertsonian translocation and isochromosome or ring chromosome are the other 2 possible causes of trisomy 21. Isochromosome is a condition when 2 long arms separate together instead of the long and short arm while in Robertsonian translocation. This occurs in 2% to 4% of the patients. The long arm of chromosome 21 is attached to another chromosome, mostly chromosome 14. In mosaicism, there are 2 different cell lines because of error of division after fertilization.

Congenital Cardiac Defects (CHD)

Congenital cardiac defects are by far the most common and leading cause associated with morbidity and mortality in the patients with Down syndrome especially in the first 2 years of life. Though different suggestions have been made about the geographical as well as seasonal variation in the occurrence of different types of congenital cardiac defects in trisomy 21, so far none of the results have been conclusive.

The incidence of CHD in babies born with Down syndrome is up to 50%. The most common cardiac defect associated with Down syndrome is an atrioventricular septal defect (AVSD), and this defect makes up to 40% of the congenital cardiac defects in Down syndrome. It is said to be associated with the mutation of the non-Hsa21 *CRELD1* gene, The second most common cardiac defect in Down syndrome is a ventricular septal defect (VSD), which is seen in about 32% of the patients with Down syndrome. Together with AVSD, these account for more than 50% of congenital cardiac defects in patients with Down syndrome.

Gastrointestinal (GI) Tract Abnormalities

Patients with trisomy 21 have many structural and functional disorders related to the GI tract. Structural defects can occur anywhere from the mouth to anus, and it has been found that certain defects like duodenal and small bowel atresia or stenosis, annular pancreas, imperforate anus, and Hirschsprung disease occur more commonly in these patients as compared to the general population.

Hematologic Disorders

There are several hematological disorders associated with Down syndrome. The hematological abnormalities in a newborn with Down syndrome

(HANDS) constitute neutrophilia, thrombocytopenia, and polycythemia, which are seen in 80%, 66% and 34% of Down syndrome babies respectively.

Endocrinological Disorders

Thyroid gland dysfunction is most commonly associated with Down syndrome. Hypothyroidism can be congenital or acquired at any time during life. The newborn screening program in New York has reported an increased incidence of congenital hypothyroidism in babies with Down syndrome as compared to the others. The anti-thyroid autoantibodies were found in 13% to 34% of patients with Down syndrome who had acquired hypothyroidism, and the concentration of these antibodies increased after 8 years of life. About half of the patients with Down syndrome have been shown to have subclinical hypothyroidism with elevated TSH and normal thyroxine levels.

Treatment

The management of patients with Down syndrome is multidisciplinary. Newborn with suspicion of Down syndrome, should have a karyotyping done to confirm the diagnosis. The family needs to be referred to the clinical geneticist for the genetic testing and counseling of both the parents.

Parental education is one of the foremost aspects regarding the management of Down syndrome, as parents need to be aware of the different possible conditions associated with it so that they can be diagnosed and treated appropriately. Treatment is basically symtomatic and complete recovery is not possible.

Conclusion

In summary, DS is a birth defect with huge medical and social costs and at this time there is no medical cure for DS. So, it is necessary to screen all pregnant women for DS. NIPS for fetal aneuploidy which was presented into clinical practice since November 2011 has not been yet considered as diagnostic test as false positive and false negative test results are still generated. Thus, invasive diagnostic testing such as CVS or amniocentesis, is recommended after a positive cfDNA fetal aneuploidy screening test.

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