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A REVIEW ON HEREDITARY DISEASE : DOWN SYNDROME

[1]Ms. Kalyani Gambhir Mohite, [2]Ms. Manisha B. Parhad, [3]Dr. Gajanan Sanap

[1]Student of Pharmacy, [2]Assistant Professor, [3]Principal
[1]Department of Pharmacy,
[1]Late Bhagirathi Yashwantrao Pathrikar College of Pharmacy, Pathri, Aurangabad, 431001, Maharashtra, India

Abstract: Down syndrome (DS) is a birth disorder with large medical and social costs, resulting from trisomy of entire or a part of chromosome 21. It is the most typical genetic disorder international 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 diagnosed candidate genes which are involved in the formation of specific DS functions. These advances in turn may assist to develop targeted therapy for persons with trisomy 21. Screening for DS is a crucial a part of routine prenatal care. Down syndrome (DS) is one of the extra commonly occurring genetic disorders, wherein mental retardation is mixed with nutritional diseases. It is resulting from having a 3rd copy of chromosome 21, and there exist three forms; Simple Trisomy 21, Translocation Trisomy and Mosaic Trisomy. Symptoms include intellectual disability/mental retardation, early onset of Alzheimer's disorder and the appearance of numerous phenotypic functions including narrow slanted eyes, flat nose and short stature. In addition, there are different health troubles during the body, consisting in a part of cardiac defects and thyroid function abnormalities along with nutritional disorders (i.e. overweight, obesity, hypercholesterolemia and deficiencies of nutrients and minerals). Those suffering DS have large body abnormalities and impaired brain development and function; the latter leading to impaired intellectual improvement. Many researches indicate excessive or deficient nutrient uptakes associated with making beside the point foodstuff choices, food intolerance, (e.g. celiac disease) or malabsorption.

Keywords **- Down Syndrome, Hereditary disease, DNA sequence, Chromosome 21, Fertility, Epilepsy, Thyroid disorder.**

I. INTRODUCTION

Syndrome (DS) is the most often occurring chromosomal abnormality in humans and affecting among 1 in 400-1500 babies born in different populations, depending on maternal age, and prenatal screening schedules. [1-6] DS is the common genetic cause of intellectual disabilities global and huge numbers of sufferers throughout the world encounter diverse additional health issues, which include heart defects, hematopoietic disorders and early-onset Alzheimer disease. [7-9] The syndrome is due to trisomy of the entire or a part of chromosome 21 in all or a few cells of the body and the subsequent growth in expression because of gene dosage of the trisomic genes. [10] It is coupled with mental retardation, congenital heart defects, gastrointestinal anomalies, weak neuromuscular tone, dysmorphic features of the head, neck and airways, audio vestibular and visible impairment, feature facial and physical capabilities, hematopoietic disorders and a better occurrence of different clinical disorders. The occurrence of births of children with DS will increase with the age of the mother. However, because of better fertility rates in younger women, the probability of having a child with DS will increase with the age of the mother and more than 80% of children with DS are born to women under 35 years of age. [7,11] The Down syndrome (DS) genetic disorder takes place in 1:600-700 newborns and is because of over-expression of chromosome 21, wherein instead of there are 3 copies. Many situations are related to DS along with metabolic disorders, tissue dimorphism, internal organ abnormalities, intellectual disabilities and feature phenotype features. [20,21]

Elucidating the genetic and nutritional factors that decide DS, gives a possibility for growing new treatments for either decreasing or eliminating the risk of the conditions accompanying this disorder, collectively with improving health status and quality of life.

II. HISTORICAL BACKGROUND

Approximately 2500 years ago, Bernal and Briceno thought that certain sculptures represented individuals with trisomy 21, making those potteries the primary empirical indication for the existence of the disease (Figure 1). Martinez-Frias recognized the syndrome in 500 sufferers with Alzheimer disease wherein the facial features of trisomy 21 are clearly displayed. Different scientists defined evident example of the syndrome in 15th and 16th century paintings. Esquirol wrote phenotypic description of trisomy 21 in 1838. English physician, John Langdon Down defined the phenotype of children with common features noticeable from different children with intellectual retardation. He referred them "Mongoloids" because these children looked like people from Mongolia. [12-15] This disease changed into named "Down Syndrome" in honor of John Langdon Down, the doctor who first recognized the syndrome in 1866 but till the middle of the 20 th century, the cause of DS remained unknown. The possibility that trisomy 21 might be a result of a chromosomal abnormality was suggested in 1932 by Waardenburg and Davenport. [12, 17]

Fig. 1: *Down syndrome statue representing individual with trisomy 21 related to almost 2500 years ago (16)*

III. Genetic Basis

Chromosome 21 is the smallest human autosome with forty-eight million nucleotides and depicts nearly 1–1.5% of the human genome. The length of 21q is 33.5 Mb and 21 p are 5–15 Mb. More than four hundred genes are anticipated to be on chromosome 21. Chromosome 21 has 40.06% repeat content comprising short interspersed repetitive elements (SINEs), lengthy interspersed repetitive elements (LINEs), and lengthy terminal repeats (LTRs). [3, 11, 18, 19] The most appropriate concept for the pathogenesis of trisomy 21 is the gene-dosage hypothesis, which declares that each one adjustment is because of the presence of an additional copy of chromosome 21. [12] Although it is difficult to select candidate genes for these phenotypes, data from transgenic mice suggest that only some genes on chromosome 21 may be concerned in the phenotypes of DS and a few gene products can be more sensitive to gene dosage imbalance than others. These gene products consist of morphogens, cell adhesion molecules, additives of multi-subunit proteins, ligands and their receptors, transcription regulators and transporters. A "critical region" inside 21q22 was thought to be responsible for numerous DS phenotypes inclusive of craniofacial abnormalities, congenital heart defects, clinodactyly of the 5th finger, mental retardation and numerous different features. [3,11]

IV. Characteristics Of Down Syndrome

DS is a disease of improvement arising from incomplete embryogenesis because of an additional chromosome 21 copy in the karyotype. This more chromosome is derived from an over-expression of genetic material due to a tripling of the range of genes. This phenomenon produces structural and functional disorders of the Central Nervous System (CNS), cardiovascular defects, dysfunction of the musculo-skeletal system, digestive system issues as well as metabolic issues, nutritional deficiencies, abnormal immune function, endocrine disruption (hypothalamic-pituitary-thyroid axis) and intellectual disabilities. DS children have impaired cognitive capabilities and, in maximum cases, belong to those with mild-moderate intellectual disability. Late improvement at multiple levels is determined with impediments in speech, memory, perception and social/societal integration. Those with DS are prone to degenerative adjustments in the brain that can be modest to severe. Such changes are because of oxidative harm to cells and tissue. Enzymatic disorders lead to excessive activity of peroxidases; that are linked to over-expression of the SOD-1 gene on chromosome 21. Structural dysfunctions of the mid-brain result in abnormalities for initiative taking and attention. Morphological anomalies in the sensory and association areas of the pre-frontal lobes result in impaired short-term memory and sense-associated cognitive capabilities.

Structural defects of the hippocampus motive long-time period reminiscence issues. Such degenerative adjustments withinside the mind can arise singly or together and have an effect on general body improvement in DS persons. Brain pathologies in shape and characteristic also result in discordant and late psychomotor development where there is a loss of coordinated motor motion and abnormal posture and locomotion. [20-23] One can distinguish between three varieties of DS, namely Simple Trisomy, Translocation Trisomy and Mosaic Trisomy. In the former, the body's cell nuclei have forty-seven chromosomes which consist of three pairs of chromosomes 21.

V. Nutritional Problems In Down Syndrome

Gastrointestinal tract abnormalities appear in 12% DS children and most usually consist of; duodenal atresia, Hirschprung disease, trachea-oesophageal fistula, pyloric stenosis, annular pancreas and anal/rectal atresia. Also present are defects withinside the oral cavity that include delayed or atypical teeth eruptions, angenesis (congenital absence of teeth) and malocclusion. There is also a tendency for teeth decay and periodontal disease. [24] DS children exhibit feeding difficulties like in chewing and swallowing food

boluses, insufficient nutrition and an inappropriate dietary calorific intake. Because of the numerous body defects, such children show low bodily activity levels leading to decreased every day calorific requirements as compared with their healthy peers. Studies also show that DS children select consuming foodstuffs made of easy carbohydrates of their diets and those that are smooth to chew and swallow. Fresh fruit and vegetables rarely feature of their diets because of problems in consuming and by being rejected by these children. This results in numerous nutritional deficiencies and a loss of regulating nutritional components as well as low nutritional fibre intakes a consequence of these deficiencies gives rise to constipation and slow intestinal peristalsis. Many findings indicate overweight and obesity in DS children, collectively with abnormal lipid metabolism and Type II Diabetes. [25, 26, 21, 27, 28]

DS children are frequently also born premature with low body mass and in adulthood, they've brief stature as well as over 1/2 of ending up being obese. The many defects seen in the gastro in testinal system coupled with its slow development rate (eg. the delayed coming-thru of milk teeth) result in poor uptakes of nutrients because solid foods are eaten at a later age, than is normal, while delivered into the diet. Short stature, diminished immunity and hypothyroidism are related with nutritional supplementation with zinc, which will increase DS children's appetite. This concerned about the particular and untoward nutritional alternatives made, as a consequence bring about an increased risk of obese and weight problems. [29, 30] Studies by Soler et al. from Spain, observed that almost all of subjects (n=38 with DS, aged 16-38 years) could be described through their BMI, obese and weight problems. Serum glucose and ldl cholesterol fraction concentrations have been inside normal. Levels of vitamin C and zinc in serum were lower-borderline normal.

VI. Mental Retardation and Nutritional Determinants

DS children discover it tough to concentrate, are prone to be pressured by environmental factors, have issues with specializing in objects or tasks, possess lowered capability for spontaneous action in addition to emotions and behavior being out of control, impaired sensory cognition/perception of objects, defective intellectual techniques related to interpretation, organization, memory and logical thinking. These intellectual disabilities may be measured by IQ and it is discovered that during maximum instances such outcomes are both rather modest (with inside the 50-70 IQ range) or limited (IQ of 35 – 50). The IQ test assesses the DS child's ability to deduce, think (which includes being creative) and interpret. It is visible that IQ levels lower with age coupled with speech impediments, reminiscence loss and a distorted belief. [36] Vitamin and mineral deficiencies arise in DS children, in particular for the B vitamins group (i.e. B1, B2, B6, B12 and folic acid), which can be responsible for intellectual development. These deficiencies in DS children bring about intellectual disabilities.

Vitamin B1 deficiency causes weakness, constipation and reduced mobility, while B2 deficiency outcomes in cracked lips and mouth corners, tongue alterations, bleeding gums and conjunctivitis. Vitamin B6 deficiency gives rise to mental retardation, low bodily interest and a loss of concentration. Joint deficiencies of nutrients B6 , B12 and folic acid are related to abnormal blood concentrations of homocysteine in DS children. [31, 32, 21, 33, 34] Zinc, selenium and calcium deficiencies are occurred in DS children. [17, 21, 33] The former significantly impacts thyroid metabolism, immunity, ensuring appropriate stature, nucleic acid metabolism, and gene expression and is a part of many enzymes. Zinc deficiency causes strange body growth, lowered immunity and thyroid dysregulation (specifically hypothyroidism). [35, 33] A few studies indicate useful outcomes of zinc supplementation or thru adopting a zinc rich diet. [36, 37, 38]

VII. Clinical Manifestations of Down Syndrome

The medical diagnosis of Down syndrome is not hard for knowledgeable physicians because of the characteristic gestalt of these patients. Patients are normally diagnosed at start or quickly thereafter. However, the diagnosis may be challenging in premature babies, a few older patients, certain ethnic groups, and in mosaicism. Each character with Down syndrome has distinct healthcare needs. Key diagnostic functions are the distinctive physical appearance, bad growth and developmental delay. The signs and signs and symptoms can be variable.

VIII. Physical Appearance

- Individuals with Down syndrome will have the subsequent physical features-
- Brachycephaly with flat occiput, extensive open fontanel & Flat facial profile,
- Flat nasal bridge & Protruding tongue,
- Small mouth & Dysplastic,
- Small, low set ears & Upward slant of palpebral fissures,
- Epicanthic folds, squint,
- Speckled iris, palebrae 'purse' on giggling or crying & Short and extensive neck,
- Considerable neck skin & Short and extensive hands,
- Short and broad fingers,
- Small center phalanx of fifth finger (clinodactyly),
- Simian crease (single palmer crease) & Increased area among 1 and a pair of toes (sandal gap) & Hypotonia,
- Hyper-extensibility/hyper-flexibility,
- Loss of Moro reflex.

IX. Growth

Children with Down syndrome usually have low birth weight, and poor growth velocity specifically at some stage in the preliminary years, partially contributed by feeding issues because of hypotonia and a small oral hollow space or due to the co-morbid situations which include cardiovascular issues and/or different gastrointestinal issues. Thereafter, the tendency toward development of obesity will increase with age and is quite common among adults with Down syndrome. The elements responsible for obesity include related hypothyroidism, excessive leptin levels, and poor basal metabolic rate. Though the Indian growth charts are not to be had, growth monitoring may be executed via the presently to be had Western Down syndrome growth charts. [39] Regular growth tracking in the preliminary years and then yearly throughout childhood would be useful in early identity of under vitamins and obesity in those children. [40, 41] There are currently no recommendations for the use of GH therapy in Down syndrome. Appropriate management of the underlying gastrointestinal conditions and hypothyroidism together with balanced diet are beneficial in

maintaining suitable weight for the age. Age suitable exercises and dietary management are useful for avoiding excessive weight gain.

X. Developmental Delay And Neurobehavioral Problems

Variable degree of developmental delay and hypotonia is a regular function in all sufferers with Down syndrome. The majority has an intelligence quotient (IQ) withinside the mild (50–70) to moderate range (35–50). Children with Down syndrome display low scores on motor, adaptive, feeding, toilet training, sleep and social improvement at every age compared to ordinary children. Motor improvement calls for approximately double the time required through a median child. They have negative language and conversation abilties broadly speaking because of speech delay, negative articulation because of the narrow oral cavity, and shortage of comprehension of language. Overall, those patients usually have pleasant behavior, are caring, affectionate, and pretty social. Some of them are song lovers. Increasingly, sufferers with Down syndrome are being recognized with autistic traits, feature functions being weird stereotype behavior, anxiety, and social withdrawal. [42] About 7 % of DS patients could have autism manifesting as early as 2 or 3 y of age. [43] Almost 100 % of the patients with Down syndrome show neuropathologic functions of Alzheimer disease through 40 y. [44]

XI. Diagnosis

1. POSTNATAL DIAGNOSIS

Although the diagnosis of Down syndrome is especially clinical, the gold popular remains the chromosomal analysis that indicates a further copy of chromosome 21. Chromosomal evaluation is now extensively available in India and can be completed on heparinised blood. Results are available in about 2–3 wk. Molecular cytogenetic techniques like quantitative fluorescent polymerase chain reaction (QF PCR) and interphase fluorescence in situ hybridization (FISH) can provide rapid diagnosis in 2 d and are sometimes wanted in small or premature neonates with a few suspicions of DS.

2. ANTENATAL SCREENING AND DIAGNOSIS

Antenatal screening for Down syndrome is a beneficial test that detects the probability of babies being born with Down syndrome. The American College of Obstetrics and Gynecology (ACOG) and the American College of Medical Genetics (ACMG) recommends antenatal screening for ladies of all age groups. [45, 46] Antenatal screening can be done both for the duration of the first trimester or second trimester relying upon the supply of the check and the timing of the primary go to by a pregnant lady. First trimester screening incorporates maternal age hazard, nuchal translucency measurement by ultrasound together with maternal serum human chorionic gonadotropin (β-hCG) and pregnancy- related plasma protein A (PAPP-A) ranges among eleven and thirteen completed weeks. The detection charge of the primary trimester display screen varies among 80 % and 82 % at a false positive rate of 3%. [47] Amongst the second one trimester screening, quadruple check is favored to triple check. It consists of maternal age hazard and estimation of maternal serum hCG, unconjugated estriol, α –fetoprotein (AFP), and inhibin A ranges among 15 and 19 wk. If blended with 18 wk anomaly scan, the detection charge is about 80 % at a false tremendous charge of 3 %. [47] If the hazard for Down syndrome exceeds the cutoff of 1:250, prenatal prognosis both by chorionic villi sampling at 11– 12 wk or amniocentesis 16–18 wk can be presented to examine the fetal chromosomes. The outcomes are typically to be had in 2– 3 wk. Rapid prenatal diagnosis in 48 h also can be furnished the usage of QF PCR or interphase FISH.

XII. Complications

Children with Down syndrome can also have additional medical complications which can affect their development. These include hypothyroidism, eye problems including refractory errors, epilepsy, deafness and otitis media, obstructive sleep apnea, congenital heart disease, gastrointestinal malformations, celiac disease, atlantoaxial dislocation, and transient myeloproliferative disorders. The presence of these complications requires extra care and medical attention. A multidisciplinary team involving pediatrician, developmental specialist, psychologists, neurologists, cardiologists, ophthalmologist, ENT specialist, speech therapist, physical and occupational therapist is essential for the best outcome. Health supervision guidelines for individuals with Down syndrome from the American Academy of Pediatrics[40] are a useful reference for specialized management and monitoring across various age groups. provides a summary of co-morbidities, their management and monitoring.

- **Congenital Heart Disease**

It is seen in approximately 50 % of people with DS, the most common being atrioventricular septal defect (AVSD) and peri membranous ventricular septal defects followed by, patent ductus arteriosus, atrial septal illness and Fallot tetralogy. [48, 49] Presence of congenital heart disease is an important thing for survival. [50] Individuals with DS should go through a complete clinical evaluation along with ECG and ECHO with common follow-up in the presence of congenital heart illness. The surgical repair of cardiac defects in individuals with Down syndrome has become a routine now and is desirable by 6 months. [51] Nevertheless, medical management and maintenance of the adequate vitamins status of the child stays the cornerstone until cardiac surgery and even thereafter.

- **Gastrointestinal Malformations**

GI malformations along with duodenal atresia (10 %), Hirschsprung disease (1–3 %), gastrointestinal reflux disease (GERD) and anal stenosis/atresia (1–4 %) can be visible in children with Down syndrome. [41, 44] Chronic constipation, belly pain, recurrent diarrhea and indigestion are common amongst those children. Celiac sickness (CD) is visible in approximately 5–12 % youngsters with Down syndrome. [52] Surgical treatment of gastrointestinal malformations, anti-reflux routine for GERD, gluten free diet for CD and measures for chronic constipation not because of Hirschsprung disease remains similar to for the general population.

- **Ophthalmological Problems**

Ophthalmological problems together with refractive errors (50 %), strabismus (20–47 %), cataracts (15 %), nystagmus (10 %), nasolacrimal duct obstruction, blepharitis (30 %), keratoconus, disorder in accommodation and retinal anomalies are quite not unusualplace in children with Down syndrome. [40, 41, 44] Untreated refractive mistakes can reason amblyopia among three and

five years of age. Visual problems can have an effect on the learning capability of children with DS. Early and well-timed eye evaluation for cataract and refractive errors is helpful. Ear Problems and Hearing Loss Hearing loss may be conductive or sensorineural and is seen in about 75 % of children with DS. The majority of these people have serous otitis media. Undetected hearing loss can similarly interfere with speech and academic efforts. A complete hearing evaluation with brainstem auditory evoked response (BERA) or oto acoustic emission (OAE), and tymapanometry should be executed at regular intervals. As approximately 2/3rd of those people are at risk of obstructive sleep apnea, an assessment with in a single day polysomnography need to be finished in all kids with the aid of using the age of 3–4 year.

- **Thyroid Disorders [40, 41, 46]**

Twenty to forty percent of children with DS can have thyroid abnormalities along with congenital hypothyroidism (1.8–3.6 %), autoimmune thyroiditis (0.3–1.4 %), Graves' disease (2.5 %) and compensated hypothyroidism (25.3–32.9 %). Thyroid function checks are recommended twice withinside the first year after which once a year. Presence of hypothyroidism requires long time substitute with L-thyroxine with frequent blood monitoring.

- **Epilepsy**

The mentioned occurrence of epilepsy in Down syndrome is 1– 13 % with infantile spasms (IS) or West syndrome (WS) being more common than the general population and requires standard treatment.

- **Fertility**

Individuals with Down syndrome have comparable onset of puberty like usually evolved adolescents however have decreased fertility. Most women are capable of hold menstrual hygiene. In the presence of intense retardation, medically induced amenorrhea or in rare circumstances hysterectomy can be an option. Most adult males are infertile.

- **Musculoskeletal Problems**

About 10–30 % of children with DS have atlantoaxial instability, which can be symptomatic in 1–2%. [53] There isn't anyt any proof of benefit for ordinary cervical spine X-rays in asymptomatic children with DS because of loss of predictability and assurance with plain X-rays. These children, however, ought to keep away from football, gymnastics, and trampoline because the hazard for spinal cord damage is expanded with those games. [40] A exact neurological evaluation and cervical spine X-rays in neutral, flexion and extension are wanted withinside the presence of threat signs along with neck pain, torticollis, radicular pain, common falls, alternate in bowel or bladder feature and signs of myelopathy like spasticity or alternate in tone and hyperreflexia etc. and require early surgical intervention. [40] Hemato-oncological Problems. [40, 44] Children with Down syndrome have expanded prevalence of iron deficiency anemia and are at an expanded hazard of developing acute leukemia. About 1 in 100 children with Down syndrome are prone to growing acute lymphocytic and acute non-lymphocytic leukemia. It is usually recommended to do a complete blood count in first 3 month and then yearly. Treatment for leukemia remains the same.

XIII. Use of Nanosuspension Drugs in Different Diseases

Till date there is no therapy for the Down syndrome, however, those children can stay a healthy, happy and relatively independent lifestyles with the aid of using the usage of following measures –

1. Initiation of early stimulation or intervention to enhance their standard developmental skills
2. Providing appropriate domestic surroundings and parental care
3. Formation of training and parental help agencies for sharing their experiences.
4. Availability of appropriate, well timed and specialized hospital therapy via all ages.

The development withinside the developmental status and conduct is rather based upon the associated co-morbidities, socioeconomic status. [54]

XIV. Conclusion

In summary, DS is a birth disorder with huge clinical and social costs and at this time there may be no clinical remedy for DS. So, it is essential to display all pregnant women for DS. NIPS for fetal aneuploidy which was presented into scientific practice since November 2011 has not been but taken into consideration as diagnostic test as false positive and false negative test consequences are still generated. Thus, invasive diagnostic testing together with CVS or amniocentesis, is suggested after a positive cfDNA fetal aneuploidy screening test. Till date, no magic bullet has been evolved to enhance the cognition in these children, however an effective early stimulation therapy, behavioral intervention, high quality domestic environment, education and vocational training of children with Down syndrome are beneficial in enhancing the general functioning and productiveness of these children.

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