International Journal Dental and Medical Sciences Research
Volume 3, Issue 1, Jan-Feb 2021 pp 805-810 www.ijdmsrjournal.com ISSN: 2582-6018

A Current Knowledge of "Down Syndrome: A Review"

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Submitted: 25-01-2021 Revised: 05-02-2021 Accepted: 08-02-2021

ABSTRACT: Down syndrome (DS) is one of the commonest disorders with huge medical and social cost. DS is associated with number of phenotypes including congenital heart defects, leukemia; Alzheimer's disease etc.DS individuals are affected by these phenotypes to a variable extent thus understanding the cause of this variation is a key challenge. In the present review article, we emphasize an types of Down syndrome, Genetics of DS, Epidemiology of DS, clinical features, screening and management and treatment of DS.Moreover, we have also reviewed various prenatal diagnostic method from karyotyping to rapid molecular methods - MLPA, FISH, QF-PCR, PSQ, NGS and noninvasive prenatal diagnosis. The scope of this article is firmly on providing the basic information in DS. The electronic database included Pub Med, Medline, Science Direct, Goggle Scholar using terms Down syndrome and trisomy 21. Relevant articles published in English on reference lists were identified and retrieved from electronic and print journals.

I. INTRODUCTION

Down's syndrome ,also called Trisomy 21.According to the National Institute of Child Health and Human Development (1), Down syndrome (DS) occurs in approximately 1 in 800 newborns, it is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21(47 chromosomes).In late 19th century an English physician whose name was John Langdon down gave the first concept of down`s syndrome, due to his discovery he was called as "father of this disease" and named derived from his name. A French physician Jerome in 1959 observed 47 chromosomes in patients with Down`s syndrome instead of 46.

In 2000, scientists discovered that in 21 chromosome there are 329 Genes which cause Down`s syndrome.[2]

It is one of the most leading causes of intellectual disability and millions of these patients face various health issues including learning and memory, congenital heart diseases(CHD), Alzheimer's diseases (AD), leukemia, cancers and Hirschprung disease(HD).The incidence of trisomy is influenced by maternal age and differs in population (between 1 in 319 and 1 in 1000 live births).[3-6]Trisomic fetuses are at elevated risk of miscarriages and DS people have increased incidence of developing several medical conditions[7]. Recent advancement in medical treatment with social support has increased the life expectancy for DS population. In developed countries, the average life span for DS population is 55 years [8].

The aim of this article is to present a narrative overview of DS. The review comprises an introduction and types of Down syndrome, Genetics of DS, epidemiology of DS, clinical features, screening and management and treatment of DS. The scope of this article is firmly on providing the basic information in DS. The electronic database included Pub Med, Medline, Science Direct, Goggle Scholar using terms Down syndrome and trisomy 21. Relevant articles published in English on reference lists were identified and retrieved from electronic and print journals.

II. REVIEW:

TYPES OF DOWN SYNDROME:

Three variants of DS are as follows:

a) **Mosaic Down`s syndrome:** Is the least common pattern of transmission of DS, occurring in 1-2% of people with DS and the error in cell division occurs after fertilization. Affected individuals have mixture of 47 or 46 chromosomes, an extra chromosome is present in 47 containing group. The greater number of normal cells in DS, the higher the chances of higher cognitive functions, with a possibility of less intellectual impairment.[9]This type of DS is not inherited, and it is estimated that 1-2% of people with DS are mosaic.[10,11]

b) **Translocation**: It occurs before fertilization where a part of an extra copy of chromosome 21 breaks off during cell division and becomes translocated to another chromosome in the egg or sperm cell. Affected individuals have two normal copies of chromosome 21, in addition to an extra attached chromosome 21. If this happens with change of genetic material or joining of entire chromosome with another, then the individual is said to have a balanced translocation. In this case, the individual will be clinically normal although there is still a risk of producing chromosomally unbalanced translocation as the sperm or ova from individuals with balanced translocation have a high risk of producing an abnormal offspring. DS due to translocation is the only variant that occurs independent of maternal age and may be inherited from either parent. Approximately 4% of people with DS have translocation, which may either be reciprocal or Robertsonian. Reciprocal translocations are the most common type and involve an exchange of chromosome between any of the different types, for example, between chromosome 1 and chromosome 9. Robertsonian translocations only involve exchanges among chromosome numbers 13, 14, 15, 21 and 22.[10,11]

c) **Non disjunction Down`s syndrome**: Trisomy 21 is most common type of DS. The error begin in either the sperm or the egg , with the presence of the extra chromosome before the egg and sperm unite. Trisomy 21 compromises about 95% of all cases. Non disjunction causing Trisomy 21 is of maternal origin in about 88% of cases and occurs more frequently in older cells, which accounts for older women giving birth to offspring with Trisomy 21.[12,13,14]

GENETICS OF THE DS

Human Chromosome 21

DS complex phenotype results from dosage imbalance of genes located on human chromosome 21(Hsa 21). The genetic nature of DS together with the relatively small size of Hsa 21 encouraged scientist to concentrate efforts towards the complete characterization of this chromosome in the past few years. The length of 21q is 33.5 Mb [15] and 21 p is 5–15 Mb [16]. A total 225 genes was estimated when initial sequence of 21q was published [16]. Hsa 21 has 40.06% repeat content out of which the repeat content of SINE's, LINE's, and LTR are 10.84%, 15.15%,9.21% respectively.

The most common cause of having a DS babies is presence extra copy chromosome 21 resulting in trisomy. The other causes can be Robertsonian translocation and isochromosomal or ring chromosome. Isochromosome is a term used to describe a condition in which two long arms of chromosome separate together rather than thelong and short arm separating together during egg sperm development. Trisomy 21 (karyotype 47, XX, + 21 for females and 47, XY, + 21 for males) is caused by a failure of the chromosome 21 to separate during egg or sperm development. In Robertsonian translocation which occurs only in 2-4% of the cases, the long arm of the chromosome 21 is attached to another chromosome (generally chromosome 14). While mosaicism deals with the error or misdivision occurs after fertilization at some point during cell division. Due to this people with mosaic DS have two cell lineages which contribute to tissues and organs of individuals with Mosacism (one with the normal number of chromosomes, and other one with an extra number 21) [17].

EPIDEMIOLOGY OF DS:

Includes risk factors, incidence and prevalence estimates has been documented extensively.

The risk factors for trisomy 21 include AMA, altered or aberrant recombination, occurrence of a previous trisomy birth and environmental factors.

Advancing maternal age and aberrant recombination remain the only conclusive and well-documented risk factors for DS pregnancy.[12,13,18] The risk of having a child with DS increases with AMA, which has been linked to biological ageing of the ovaries.[19] About 85% – 88% of DS is associated with errors from the maternal egg, about 5% – 9% originates from the paternal sperm while the remaining 1% – 3% are attributed to mitotic cell division errors that happen after fertilization.[18,20]The AMA risk factor in DS applies mainly to the trisomy 21 variant of DS. Although AMA is the primary risk factor for DS birth, due to higher birth rates in younger women, about 80% of children with DS are born to women under 35 years of age.[21]

Recurrence risk as a factor expresses the possibility of women who had prior DS births to have subsequent ones. For women who had prior trisomy

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21 child birth, there is an approximately 1% recurrence risk of having another child with trisomy 21. The carriers of a balanced translocation of chromosome 21 are also documented risk factors for DS pregnancy.[21]

Another risk factor in DS conception is altered 'recombination patterns'. Although trisomy 21 is due mainly to errors in the final stage (chromosome segregation) of meiosis, considerable evidence has shown that errors in the second stage (recombination stage) prepare the cell for non-disjunction. Thus, reduced recombination invariably results in increased frequency of non-disjunction. Evidence from both cytogenetic and epidemiological studies suggests that various environmental and occupational exposures are also risk factors that may increase the chances of trisomy 21 birth. These factors include alcohol and nicotine, medications (oral contraceptives and spermicides, hormonal therapy, radiation therapy and fertility medications), toxic wastes and infections.[21]

Clinical Features of DS

DS is a multisystem disorder that affects the individual physically, medically and psychologically.

Although the phenotypic features of DS vary from person to person, individuals with DS are more likely to experience a number of medical conditions, including, neurological, cognitive, cardiac, and orthopedic conditions. These include intellectual disability, which is always present in DS although the severity varies. Other medical complications include increased prevalence of Alzheimer's disease, leukemia, congenital heart disease, dementia, seizure disorders, sleep apnea, excess mobility of the atlas and axis, gastrointestinal concerns, vision and hearing problems, endocrine disorders, and musculoskeletal abnormalities (22,23,24,25,26)

The head, face and neck features include brachycephaly (disproportionately shorter or small head or skull shape), unusually round face, short neck, low-set, small ears, flat nasal bridge, microgenia (an abnormally small chin), macroglossia (protruding or oversized tongue) due to small oral cavity, small chin, almond shape to the eyes caused by an epicanthic fold of the eyelid and oblique palpebral fissures. Other features include shorter limbs, a single transverse palmar crease (a single instead of a double crease across one or both palms), lax ligaments, excessive space between large toe and second toe, dry skin, muscle hypotonia (poor muscle tone) and brachydactyly (shorter fingers and toes). Ocular and visual features of DS include high refractive errors, amblyopia and strabismus, accommodative and vergence anomalies, ptosis, blepharitis, nasolacrimal duct obstruction, nystagmus, keratoconus, speckling of the iris (Brushfield's spots), cataracts, glaucoma and retinovascular anomalies.(26,27)

The major health condition associated with DS are summarized in Table 1.(27,28,29,30,31)

Systems	**Conditions**
Cardiac defects	Incidence of congenital heart disease in DS is between 44% and 50%. Commonly atrial septal (wall of the heart) defects and ventricular septa defects
Cognitive	Mainly intellectual disability which affects learning, memory, and language that leads to mild-to profound impairment in intellectual functioning
Gastrointestinal	Commonly feeding difficulties and gastro-oesophageal reflux
Dermatological	Dry skin, folliculitis, vitiligo
Neurology	Developmental deficiencies; mainly intellectual disability
Respiratory	Due to an enlarged tongue, uvula and soft palate predisposes towards obstruction
Central nervous system	Dementia and Alzheimer's disease in adults
Ear nose and throat	Conductive and sensori-neural hearing loss, sleep-related breathing disorders (such as sleep apnea) and chronic catarrh
Orthopaedic	Cervical spine disorders, joint and muscle problems
Reproduction	Impaired fertility both genders; males are usually unable to father children, while females have

	fertility and birth problems including miscarriages, premature births and difficult labor
Dental	Include caries and malocclusion
Endocrine/growth anomalies	Commonly hypothyroidism, hyperthyroidism, obesity and diabetes, impaired stimulation of growth hormone.
Haematological/ oncology	Mainly leukaemia
Immunological	Immune dysfunction, autoimmune disease such as arthropathy, vitiligo, alopecia Increased susceptibility to infections than normal children
Neuropsychiatric/behavioural	Common neuropsychiatric problems in DS children include epilepsies, autistic spectrum disorder, depressive illness, dementia (adults), attention deficit hyperactivity disorder, conduct/oppositional disorder (5.4%), or aggressive behaviour.

Screening & Diagnosis of DS:

There are two types of screening tests, namely, Screening and Diagnostic tests.

Screening Test:

In first trimester USG and complete blood count is done to evaluate pseudopositive testify test. In second trimester ultrasonagraphy and Quadruple Marker Screen (qms) is done to valuate NTD (Neural tube defects) and DS. The prenatal screenings do not give definite results but provide the probability of a fetus having DS. If the screening tests give positive findings for Ds, a pregnancy may have DS, a diagnostic test is performed to confirm if the fetus has DS.

Diagnostic Test:

Chorionic Villus sampling, Amniocentesis, Cordocentesis or percutaneous umbilical blood sampling. Amniocentesis and Chorionic villi sampling are quite reliable but offers risk of miscarriage of between 0.5 to 1%.[32]The other methods used for Prenatal diagnosis in which cytogenetic analysis is widely used in different countries. They are Rapid aneuploidy testing methods, Noninvasive Prenatal diagnosis, FISH (Fluorescence in situ hybridization), QF-PCR (Quantitative fluorescent- polymerase chain reaction), PSQ (Paralogous sequence quantification), MLPA (multiplex probe ligation assay)and NGS(Next generation Sequencing). Therefore a diagnostic, unlike screening test provides a definite diagnosis with almost 100% accuracy.[21]

Treatment& Management of the disease

One of the signs of DS is the variability in the way that the condition affects people with DS. With the third 21st chromosome existing in every cell, it is not surprising to find that every system in the body is affected in some way. However, not every child with DS has the same problems or associated conditions. Parents of children with DS should be aware of these possible conditions so they can be diagnosed and treated quickly and appropriately.

Timely surgical treatment of cardiac defects during first 6 months of life may prevent from serious complications. Congenital cataracts occur in about 3% of children and must be extracted soon after birth to allow light to reach the retina. A balance diet and regular exercise are needed to maintain appropriate weight. Feeding problems and failure to thrive usually improve after car- diac surgery. A DS child should have regular check up from various consultants.

It is treated surgically, medically or different types of psychotherapies are done. Following method of treatment can be done to avoid complication in adulthood

- Clinical geneticist - Referral to a genetic counseling program is highly desirable
- Developmental pediatrician
- Cardiologist - Early cardiologic evaluation is crucial for diagnosing and treating congenital heart defects, which occur in as many as 60% of these patients
- Pediatric pneumonologist -Recurrent respiratory tract infections are common in patients with DS
- Ophthalmologist
- Neurologist/Neurosurgeon – As many as 10% of patients with DS have epilepsy; therefore, neurologic evaluation may be needed
- Orthopedic specialist

- Child psychiatrist - A child psychiatrist should lead liaison interventions, family therapies, and psychometric evaluations
- Physical and occupational Psychotherapist
- Speech-Psychotherapist
- Audiologist

III. CONCLUSION:

DS or Trisomy 21, being the most common chromosomal abnormality among live born infants, is associated with a number of congenital malformations. Several theories have been put forward to increase our understanding in phenotype and genotype correlation. A "critical region" within 21q22 was believed to be responsible for several DS pheno-types including craniofacial abnormalities, congenital heart defects of the endocardial cushions, clinodactyly of the fifth finger and mental retardation and several other features. Since various clinical conditions are associated with DS, hence the management of these patients requires an organized multidisciplinary approach and continuous monitoring of these patients which has been discussed in this review article.

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