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DOWN SYNDROME CHILDREN - AN UPDATE

Editor:
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CHAPTER 2

Genetics of Down Syndrome: An Update

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Abstract: Since the discovery of the chromosomal basis of Down syndrome (DS) in 1959, researches are still trying to understand the genetic basis of this particular unique common disorder that cannot be simply explained by an additional chromosome 21. Recent advances in molecular genetics had shed the light on several genes peculiar to this disorder like DYRK1A involved in cognitive dysfunctions and GATA1 involved in transient myeloproliferative disease. Some of these genes are actually beneficial when found in excess like COL18A1 which encodes endostatin, a potent angiogenesis inhibitor that inhibit the progression of solid tissue tumors and thus may have a potential therapeutic effect as anticancer therapy, as an anti-inflammatory agent and for protection against diabetic retinopathy. Gene therapy - or better to say chromosome therapy - for patients with DS is a recent break through where scientists were able to silence the extra chromosome and reverse the neuron proliferation dysfunction. This will not only help patients with DS but could be applied to all chromosomal trisomies. By understanding the pathogenetic mechanisms of DS, the near future is holding hope not only for treatment of DS cognitive dysfunction but also cures for solid tumours and certain disorders that will be done through inducing trisomy 21 in affected cells!

Keywords: AIRE, Blessing effect, Chromosomes, Cytogenetics, Down syndrome, DSCR-1, DYRK1A, Endostatin, GATA1, Gene therapy, JAK2, Lucky mothers, Molecular, Mosaicism, Nondisjunction, Overexpression, Polymorphism, Robertsonian translocation, TAM, Trisomy 21.

1. INTRODUCTION: CHROMOSOMAL BASIS OF DOWN SYNDROME

Lejeune *et al*. 1959 are credited with the discovery of the chromosomal basis of Down syndrome (DS) [1]. Shortly thereafter, Polani *et al*. 1960, discovered translocation DS in the daughter of a 21-year-old mother because they had

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Mohammed Al-Biltagi (Ed)

reasoned that some individuals may be affected through a separate, maternal-independent chromosomal mechanism [2]. In the following year, Clark *et al*. 1961 reported mosaic DS, in a 2 year-old girl with physical stigmata of DS but near normal intelligence [3]. The most common chromosomal anomaly in patients with DS is "trisomy" in which there is an additional copy of chromosome 21. This is present in 95% of patients followed by translocation (in 4-5%) in which the extra-copy of chromosome 21 is translocated on one of the acrocentric chromosomes (mostly 14 or 21) [4, 5]. Mosaic DS is least common, found in only 1% of patients [6].

2. ETIOLOGY AND ORIGIN OF EXTRA CHROMOSOME 21

2.1. Nondisjunction Trisomy 21

Finding the origin of the extra copy of chromosome 21 with highly informative DNA markers will not alter the scenario of genetic counseling; it will only confirm the already known fact that the meiotic error in the maternal (not paternal) chromosomes is the origin of the extra copy. Ironically, fetuses with trisomy 21 where the origin of the extra-copy is of maternal origin have an advantage of intrauterine survival. Thus it might be only a scientific interest to determine the origin in spontaneous abortions of trisomy 21 fetuses [7].

Trisomy 21 (also known as chromosome nondisjunction) is caused by failure of the two similar chromosomes (21)s to separate (segregate) properly during meiosis. The vast majority occurs in oocytes [8] specifically during meiosis I (MI) [9]. Causes of this error have been thoroughly investigated and the most significant risk factor found was advanced maternal age in which the error occurs during oogenesis and for chromosome 21, it can occur in both meiosis I and meiosis II [10].

Other risk factors suggested include accumulation of environmental toxic elements which can damage the meiotic machinery of the oocytes causing chromosome nondisjunction. This can occur through different mechanisms; metals acts possibly through epigenetic mechanism while very small particles (nano-sized) might act directly with mitotic and meiotic machinery and with subcellular components. Also, cytotoxic drugs used in different healthcare

occupations (causing inhibition of cell growth), continuous exposure to electromagnetic fields (with a limited evidence of causing aneuploidy) have been suggested as other environmental risk factors that may act with aging or genetic predisposition to produce nondisjunction [11, 12]. Some investigators suggested that reactive oxygen species produced by metabolism could diminish the oocyte quality [12].

More than a decade ago, Torfs and Christianson in 2003 suggested an association between low maternal socioeconomic status and the occurrence of non-disjunction of chromosome 21 [13]. Recently, this theory was reinvestigated and confirmed by Hunter *et al*. 2013 but they did not elucidate the actual factors that account for the increased incidence of nondisjunction (whether it is the poor nutrition or the environmental exposure) [14]. Another possible mechanism was investigated by Ghosh *et al*. 2010 who suggested that shorter telomere length contributes by one way or another to the meiosis I or II error and subsequently non disjunction. They found the telomeres of the older mothers of DS are relatively shorter (making them genetically older) compared to the control mothers of the same age with normal euploid babies [15].

2.2. Robertsonian Translocation

The second commonest chromosomal anomalies in DS (4%) is the Robertsonian translocation where the long arm of one of the acrocentric chromosomes (13, 14, 15, 21) is translocated to the long arm of chromosome 21 and so the number of chromosomes will be 46 and not 47 (unbalanced translocation). The advanced maternal age is not a risk factor for this abnormality but if one parent is a carrier for translocation (balanced carrier), the recurrence risk is increased and so cytogenetic analysis for both parents is mandatory to provide accurate genetic counseling [16].

The origin of denovo t (21; 21) DS are usually different from the other reciprocal translocation. For the majority of such chromosomes are not centric fusion or whole arm exchange chromosomes, rather they are isochromosomes (iso 21q) resulting from fusion of sister chromatids [17, 18]. Whether isochromosomes arise during oogenesis is not established, and it is argued that isochromosomes arise

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FOREWORD

English physician John Langdon Down was among the first to describe the disorder now called Down syndrome (DS) about 150 years ago. In 1959, Dr. Jerome Lejeune, a French scientist, reported that Down syndrome results from presence of an extra copy of human chromosome 21. Now we know that Down syndrome is the most common live-compatible human chromosomal abnormality, occurring in 1 in 700-800 newborns. Latest studies have shown that pregnancy termination rates following prenatal diagnoses have decreased the incidence of DS in recent years in some population groups, which may reflect advances in medical interventions for people with Down syndrome and progresses in educational and social support for their families. These advances have also significantly extended the life expectancy for people with Down syndrome. Therefore, Down syndrome will continue to affect a significant size of our population and thus remain as a major public health challenge in the future.

Due to the impacts of presence of an additional copy of the whole chromosome 21, individuals with Down syndrome exhibited a constellation of developmental abnormalities affecting many organ systems. Congenital heart defects, including atrioventricular defects, are discovered in about 50% of kids with Down syndrome. Meanwhile; about 10% of children with Down syndrome develop transient myeloproliferative disorder, and approximately 30% of these patients develop acute megakaryoblastic leukemia, which equates to just about 500-fold greater risk of having acute megakaryoblastic leukemia. Human trisomy 21 is the most frequent genetic cause for developmental cognitive disabilities. The brains of individuals with DS over the age of 40 show the neuropathological changes of Alzheimer's disease.

The landmark discovery of human trisomy 21 as the chromosomal basis for Down syndrome has also positioned this disorder as the most complex human genetic disease compatible with postnatal survival. As a result, progress in Down syndrome research has been slow until 1990s when development of mouse models of Down syndrome, particularly Ts65Dn, enabled scientists to explore the disorder at the molecular, cellular, physiological and organismal levels. The convergence of recent advances in mammalian genome sequencing and chromosome engineering technology has opened up an unprecedented opportunity for unraveling the mechanisms underlying abnormal phenotypes in Down syndrome by generating and analyzing new mouse mutants with precise duplications and deletions of human chromosome 21 orthologous regions. Amidst these remarkable advances related to Down syndrome research, the publication of the e-book "Down syndrome children – an update" edited by Dr. Mohammed Al-Biltagi is welcome news, which will provide the latest information on medically important areas associated with Down syndrome, including the

prevalence, genetics, infection in children with Down syndrome, cardiac, skeletal and dental abnormalities, biochemical, respiratory, gastrointestinal and psychological changes, neonatal, neurological, hematological problems, as well as problems with anesthesia. Such a timely update will surely benefit all of us who care so much about

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PREFACE

Down syndrome is the commonest genetic disease in the world; affecting all countries, all races, and both sexes. Since the comprehensive description of clinical features of the syndrome in 1866 by John Langdon Down; and its genetic basis in 1959, researches are still trying to study various aspects of this syndrome to improve the health and the quality of life of the affected people. This book **"Down syndrome children - An update"** is a compilation of Twelve excellent chapters, contributed by established researchers in the field and covering different aspects of the problems that a child with Down syndrome can enface.

In the first chapter; Dr. Al-Biltagi shed some light on the epidemiology of DS, the factors affecting the risk of Down syndrome, and the prevalence of DS in the different parts of the world. In chapter 2; Dr. Solaf discussed the genetic basis of this syndrome together and the role of different genes in development of various syndrome related diseases. Then in the third chapter; Dr. Al-Biltagi and Dr. Hagag discussed the various neonatal problems in DS. After that, Dr. Al-Biltagi and Prof. Osama Tolba shed some light on the various cardiac problems that a child with DS can have.

In the Fifth chapter, Dr. Al-Biltagi discussed the different respiratory disorders that children with Ds have and the prophylaxis against respiratory infections which are relatively common in children with DS. He also explained in the sixth chapter the different anatomical and functional gastrointestinal problems that are common in those children. At the same time, Dr. Saeed discussed in the seventh chapter, reasons for increased incidence of infection in children with DS as well as the different types of infections that children with DS are exposed to and the effect of the infection on DS and how to prevent these infections. Then Dr. El-Shanshory explained the different hematological problems that are frequently encountered in DS children in the eighth chapter. Then Dr. El-Mitwalli described the neuro-anatomic functions of the brain in DS and explained the different neurological disorders that are common in DS children in the Ninth chapter.

In the tenth chapter; Dr. Fu Yong Jiao and his colleagues described the mental development, the behavior phenotypes, the academic achievements in young people with DS as well as the psychology of sex, the various psychosocial problems in children and adolescents with DS and diagnosis, assessment and management of these disorders. In the eleventh chapter, Dr. Alasy and his colleagues described the various aspects of anesthesia related problems and their management in children with DS. Then Dr. Meakkara described the various dental problems and their management in twelfth chapter.

A great effort has been made to accomplish this book. It would not have been possible to

complete this book without the sincere efforts of the authors, and especially the staff at Bentham Science Publishers, giving their continuous support. Their patience, enthusiasm and encouragement were a greatly appreciated source of strength during its extended preparation. Perhaps of greater importance, than the book and its many contributions, were the remarkable people that formed a unique collaborative team to make it happen.

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CHAPTER 1

Epidemiology and Prevalence of Down Syndrome

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Abstract: Down syndrome (DS) is the commonest chromosomal disorders in the world; affecting all countries, all races, and both sexes. It was identified since premodern art and middle ages. The risk for DS births is multi-factorial and includes both genetic and environmental factors. The prevalence of DS could be affected by different factors including distribution of maternal age in the population, adequacy and completeness of ascertainment, accurateness of diagnosis, level of selective prenatal termination of affected pregnancies, as well as different unrecognized genetic and environmental factors. Incidence of DS is expected to be significantly high in the developing countries, probably due to the higher death rate from comorbidities in DS such as congenital cardiovascular defects. Improving survival of infants with DS because of better care especially of cardiovascular malformations will affect prevalence rather than the incidence of DS. According to World Health Organization; the predictable incidence of DS is between 1 in 1,000 to 1 in 1,100 live births all over the world. The difference in prevalence among populations or countries or in the same population over time will depend on the potential risk factors in common for that community.

Keywords: Africa, America, Arabs area, Asia, Chemical Toxins, Children, Chromosome aberrations, Consanguinity, Cytogenetic, Down syndrome, Environmental factors, Europe, Genetic Factors, Gonadal trisomy mosaicism, Incidence, Ionizing radiation, Maternal age, Paternal age, Prevalence, Smoking, Socioeconomic Status.

1. INTRODUCTION

Down syndrome (DS) is the commonest genetic disease in the world population; affecting all countries, all races, and both sexes. There are some reports that identified paintings of persons with appearance of DS in premodern art and

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paintings and from pictures from the middle ages. In the modern medicine, Jean Etienne Dominique Esquirol (1772-1840) was the first to describe this syndrome followed by Édouard Séguin who described some clinical features of DS after 6 years in 1844. However, John Langdon Down was the first to give a comprehensive description of clinical features of the syndrome in 1866. He was an English physician at the London Hospital, and gave his name to this syndrome. In 1909, Shuttleworth was the first physician who observed the association between the increased maternal age and and the increased risk of DS. However; Jérôme Jean Louis Marie Lejeune (1926-1994); French human geneticist was the first scientist who related this syndrome to trisomic aberration of chromosome 21 in 1959. After that and onward; many researches were done in a try to uncover the role of the extra chromosome 21 in relation to the phenotype of DS. Traditional epidemiological studies concerned with determination of the prevalence of DS have been conducted over the last 100 years. It was of interest for many societies and researches as regard to temporal, racial, geographical, and environmental differences in rates. The prevalence of DS differs from a country to another and sometimes from a district to another within the same country [1 - 3].

2. FACTORS AFFECTING THE RISK OF DOWN SYNDROME

The risk for DS births is multi-factorial and includes both genetic and environmental factors. To understand how a factor can affect the prevalence of DS; it is crucial both to understand the chromosomal imbalance and the genomic content of chromosome 21 and how the expression levels of these genes are altered by the presence of this third copy generally resulting from non-disjunction during the stage of meiosis of either the ovum or the sperm. With development of proper cytogenetic studies, investigators are now able to distinguish the underlying types of chromosomal errors into trisomy 21, translocations, and mosaicism (one normal cell line and one trisomic cell line). The prevalence of DS could be affected by different factors including distribution of maternal age in the population, adequacy and completeness of ascertainment, accurateness of diagnosis, level of selective prenatal termination of affected pregnancies, as well as different unrecognized genetic and environmental factors [4].

2.1. Maternal Age at Birth

Mother age at the time of pregnancy with fetus with DS is one of the most well studied factors that affect the possibility of occurrence of DS since the observation of Shuttlewort in 1909, Van der Scheer in 1927, Thurston and Jenkins 1931 and by Penrose in 1933 [5]. Increased maternal age is considered as one of the most important factors contributing to the increased risk of having DS affected fetus. Many studies described the relationship between mother age over 35 years and the increased risk of DS [6].

Many studies documented that the average maternal age at the time of pregnancy of a fetus with DS is significantly higher than that of mothers with normal euploid fetus in different populations and races [6, 7]. The likelihood of having a baby with DS is less than 1 in 1,400 for a mother under 25 years, and less than 1 in 1,000 for a mother under 30 years. The risk increased to 1 in 350 for mothers who become pregnant at age 35 and continues to increase as the woman get elder, so that by age 42, and by age 49, the chance is 1 in 60 and 1 in 12 correspondingly [8]. However, there are some studies reporting that about eighty percent of children with DS were born to young mothers with age less than 30 years [9].

Many studies showed that there was significant increase in the percent of trisomy in pregnancy losses in women over 40 years than the percent of trisomy in pregnancy losses in women less than 24 years. So, the major fundamental factor accountable for the increased infertility observed with advancing maternal age is the increase in aneuploidy [10 - 12]. Currently, the investigators are able to determine the parental source of the extra chromosome by using chromosome 21-specific DNA markers. They are also able to categorize the stage of error in meiosis whether occurred in meiosis I or meiosis II. Many studies showed that about ninety percent of errors were of maternal origin [13]. Also these studies showed that most of the errors occurred in meiosis I (which begun during the fetal life of the mother and was accomplished many years later at the time of ovulation) than in meiosis II (which is started and completed within 3–4 days at the time of ovulation) with a ratio of 3:1[14].

As a woman is getting elder; the risk for having a baby with trisomy 21 is

CHAPTER 3

Neonates with Down Syndrome

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Abstract: Neonates with DS have many co morbidities that jeopardize this critical period of life with increased morbidity and mortality. They have more incidences of congenital heart diseases, pulmonary disorders, epilepsies, gastrointestinal anomalies, hematological problems as well as feeding disorders. They need to recognize their problems and for early intervention that could improve their medical conditions as well as their quality of life.

Keywords: Amniocentesis, Airway Abnormalities, Chorionic villus sampling, Congenital heart defects, Cordocentesis, Down syndrome, Endocrine Disorders, Eye, Feeding, Free fetal DNA, Gastrointestinal, Growth, Hematologic Disorders, Neonates, Nuchal translucency, Orthopedic Disorders, Persistent pulmonary hypertension of the neonate, Prenatal screening, Prevention, Quadruple screening, Triple screen, Ultrasonography.

1. INTRODUCTION

Trisomy 21 (Down syndrome) is the most common numerical chromosomal anomalies among live born babies. Down syndrome (DS) is the most common type of developmental disability caused by a microscopically confirmable chromosomal abnormality. It affects more than 5 million people all over the world. It has a well defined characteristic typical and phenotypic features and natural history. The symptoms related to the underlying diagnosis can appear in practically every organ system. Early identification of DS in the newborn is necessary to supply adequate care for the newborns and support for their parents and family; although at times the physical features may be difficult to identify in a

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newborn especially when premature and in mosaic form of DS where there are a wide variation in expression of the disorder according to the percentage of cells that carry the extra chromosome 21, the phenotype may be milder than that of classic trisomy 21 [1]. With the modern advances of the genetic studies of chromosomes, principally chromosome 21, has led to new understanding and awareness on diseases. The capability to recognize and expect the outcome of patients with DS offers the healthcare suppliers the chance to develop individual distinctive approaches to a comprehensive care of neonates with DS [2].

2. DIAGNOSIS OF DOWN SYNDROME

2.1. Antenatal Diagnosis

Antenatal diagnosis of DS helps to achieve an informed decision-making with regard to pregnancy continuation or termination and can help the family to make an appropriate choice. There are two fundamental categories of tests available to detect DS during pregnancy; screening and diagnostic tests.

2.1.1. Prenatal Screening

Pregnancy screening for fetal aneuploidy began in the mid 1960s, using maternal age as the screening tool. Screening programs for DS are well established in many countries with recent advances in prenatal screening tests in the last decades. The pregnant women should be well educated about the benefits, safety and risk of these screening tests. Screening tests help to stratify the baby's risk of having DS and to decide the need of further diagnostic test. These tests do not offer precise and confirmed diagnosis, but they are safer than the diagnostic test for both the mother and the fetus. However, screening tests can occasionally provide false positive and false negative results with sensitivity of multiple marker screening tests for DS is between 61 and 67 % [3]. These tests are recommended for women who are of at more risk to have a pregnancy affected by DS. The benefits and disadvantages of these tests should be discussed before the pregnancy has reached 15 weeks as they are not routinely recommended. It is now achievable to provide all pregnant women with a non-invasive screening test to stratify their risk of having a fetus with aneuploidy and to determine the need for invasive prenatal diagnostic testing. A wide range of interventions has been launched to help the

pregnant women to choose the proper prenatal screening. Screening tests usually comprise a combination of a blood test, which estimates the quantity of a variety of materials in the mother's blood (*e.g*. Pregnancy-associated plasma protein A (PAPP-A), beta human chorionic gonadotropin (beta-hCG) and MS-alpha-fetoprotein (AFP) and an ultrasound [4].

There are multiple antenatal screening strategies for DS in the first and second trimesters; and usually done in combination with more than a screening tool. For example; one strategy in Belgium is to combine the nuchal translucency (NT) ultrasound measure at week 12 (weeks 11–14), the level of free-β-human chorionic gonadotropin hormone and pregnancy associated plasma protein-A, in combination with age and medical history [3]. Currently available non-invasive screening choices include maternal age combined with one of the following: (1) first trimester screening (nuchal translucency, maternal age, and maternal serum biochemical markers), (2) second trimester serum screening (maternal age and maternal serum biochemical markers), or (3) 2-step integrated screening, which includes first and second trimester serum screening with or without nuchal translucency (integrated prenatal screen, serum integrated prenatal screening, contingent, and sequential) [5].

2.1.1.1. Prenatal Blood Screening Tests

These tests depend on measuring the levels of various fetal or placental proteins and hormones in the pregnant lady blood. There are two main screening tests used for DS pregnancy; the combined screening test (the preferred approach) and the quadruple test for women who present later during the pregnancy or where combined screening cannot be carried out. The combined screening test combines the result of the nuchal translucency (NT) scan with the result of blood tests for Pregnancy Associated Plasma Protein A (PAPP-A) and Free beta human chorionic gonadotropin (beta-hCG) to stratify the relative risk of having a child with Down syndrome. The blood tests and the scan are frequently done at the same time. The chance estimation depends on the levels of these materials in the maternal blood, maternal age, her weight and the duration of pregnancy. Typically this blood test is done between 10 to 14 weeks of pregnancy. This test is used to screen only for DS and trisomy 18. On the other hand; the maternal serum levels

CHAPTER 4

Cardiovascular Disorders in Children with Down Syndrome

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Abstract: Down syndrome (DS) is commonly associated with cardiovascular disorders either congenital or acquired. Congenital cardiac diseases (CHDs) occur in about half of children with DS. They also are more liable to have pulmonary hypertension, mitral valve prolapse, aortic regurgitation and many other acquired cardiac conditions. Meanwhile, they are also of a higher risk for developing obesity than the control children which predisposes them to an increased risk of atherosclerosis. Antenatal detection of DS as well as CHDs can be detected by presence of some soft signs during routine antenatal 4-chamber view. Children with this syndrome should have echocardiographic examination in the first month of life for all neonates, before any cardiac surgery, as follow-up after cardiac surgery, for serial evaluation of pulmonary hypertension, before involvement in major non-cardiac surgery and before involvement in physical exercise as well as serial follow up for early detection of any cardiac disorder. In this chapter, prevalence, pathomechanism and methods of detection of cardiac disorders in children with DS as well as their management are discussed.

Keywords: Aberrant right subclavian artery, Atrioventricular septal defects, Cardiac functions, Children, Congenital Cardiac Diseases, DSCR1 gene, Down syndrome, Echogenic intracardiac foci, Fallout Tetralogy, Fetal echocardiography, Hypothyroidism, Mitral Valve prolapse, Nuchal translucency, Over-expression, Patent ductus arteriosus, Pathomechanism, Pericardial Effusion, Single umbilical artery, Soft signs, Ventricular septal defects.

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1. INTRODUCTION

Down syndrome is commonly associated with cardiovascular disorders either congenital or acquired. Congenital heart diseases occur in approximately half of children with DS. At the same time; children with DS who were born with normal heart at birth may furthermore develop cardiac problems in the future like pericardial effusion, pulmonary vascular disease and right cardiac failure due to airway/respiratory anomalies. Meanwhile, they are also of a higher risk for developing obesity than control children which predisposes them to an increased risk of atherosclerosis [1]. Adolescents with DS are also at increasing risk to develop mitral valve prolapse and aortic regurgitation [2]. So; the aim of this chapter is to highlight the different aspects of cardiovascular diseases in children with DS.

2. CONGENITAL HEART DISEASES (CHD)

2.1. Prevalence of Congenital Heart Diseases in Children With Down Syndrome

The incidence of CHD showed marked increase from 0.8% in normal population to reach 40-60% in DS cases and they form about one tenth of all children with congenital heart diseases. These CHDs may be simple or complex which could have deleterious effects on the affected children and their families. They may have congestive heart failure, pulmonary vascular disease, pneumonia, or failure to thrive. CHDs are the most common cause of death among those children in the first 2 years of life [3, 4].

The most common CHD observed in children with DS are Atrioventricular septal defects (AVSD; with or without other CHD) (Fig. **1**). It forms approximately 45% of all CHDs observed in DS children. The second most common CHD was ventricular septal defects (VSD; with or without other CHD) which forms approximately 35% of all CHDs observed in DS children. Isolated secundum atrial septal defect (ASD) forms 8%, isolated persistent patent ductus arteriosus (PDA) forms 7% and an isolated Fallout Tetralogy (TOF) forms 4%. Arch abnormalities (aortic coarctation, right aortic arch, aberrant right subclavian artery) constitute the remaining 1% of CHDs [5]. On the other hand, there is less

frequency of certain cardiac malformation in children with DS than non-DS children *e.g.*, heterotaxy, aortic coarctation or transposition of the great arteries which could reflect the effects of presence of 3 copies of certain a gene or genes on chromosome 21 on only specific developmental points [6].

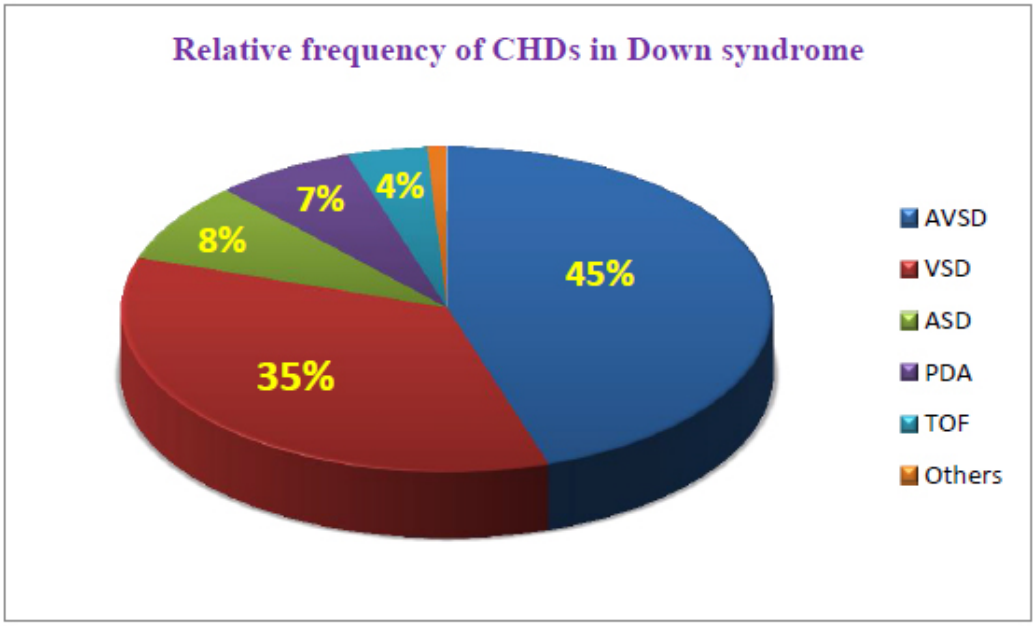

Fig. (1). Showed the relative frequency of CHDs in children with Down syndrome.

2.1.1. Factors Affecting the Rate of Congenital Cardiac Diseases in Children with Down Syndrome

Despite AVSD is the most common cardiac anomalies in children with DS, however; the relative frequency of each CHD will vary by different factors. Table **1** showed the different factors that could affect the frequency of CHDs in DS populations.

2.2. Pathomechanism of CHD in Children with DS

Development of human heart is very complex and starts very early by the 3rd week of pregnancy and develops progressively till the 8th week of pregnancy. The primitive tube develops and begins to beats at 25 days of gestation and ends in the four-chamber heart through many steps including looping, cell migration, cell

CHAPTER 5

Respiratory Problems in Children with Down Syndrome

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Abstract: Children with Down syndrome (DS) are more prone to have respiratory disorders which can be categorized into congenital structural disorders of the airways and lungs, acquired disorders, and sleep-related disorders and obstructive sleep apnea. Children with DS have a high incidence of airway anomalies; both upper and lower compared to non-DS children. The most important findings are hypoplasia of midface with dysfunction of malformed Eustachian tube, a short palate, hypoplastic nasal bones, choanal stenosis, macroglossia, enlarged adenoids and tonsils, lingual tonsils, and narrow oropharynx, and nasopharynx, abnormal oropharyngeal structures, laryngomalacia, tracheomalacia, congenital subglottic stenosis, tracheo-oesophageal fistula, bronchomalacia and branching and lung anomalies. Among the acquired respiratory disorders encountered in children with DS are respiratory infections including acute bronchiolitis due to infection with respiratory syncytial virus, pneumonia, infection with H1n1 stains of flu virus, high incidence of acute lung injury, occurrence of pulmonary hemosiderosis, increase incidence of pulmonary hypertension, GERD, and the possibility of having asthma. Sleep disorders are common and important problems, frequently under-recognized in children with DS and can be a significant distressing factor to their families. The prevalence of these disorders in children with DS is very high, particularly in boys. Vaccinations help to prevent a considerable number of infectious diseases. The immune dysfunctions of DS are not a contraindication for the currently available vaccines: their immunogenicity and safety are not significantly different from those observed in the general population.

Keywords: Adenotonsillar hypertrophy, Abronchomalacia, Children, Down syndrome, Esophageal atresia, Glue ear, Immune stimulation, Hypotonia, Laryngomalacia, Lung hypoplasia, Hypothyroidism, Macroglossia, Pulmonary

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hypertension, Reflux, Respiratory problem, Subglottic stenosis, Tracheal atresia, Tracheal bronchus, Tracheoesophageal fistula, Tracheomalacia.

1. INTRODUCTION

Children with Down syndrome (DS) suffer a major health load and troubles, especially the young children who frequently encounter cardiac and respiratory problems. DS can affect the respiratory tract (both upper and lower) in different ways and can impact upon and lower respiratory functions, giving rise to a wide variety of respiratory manifestations. Respiratory problems are common reasons for increased morbidity and mortality in children with DS. These respiratory problems include structural anomalies of the airways and lungs, glue ears, frequent lower respiratory tract infections and increased incidence of obstructive sleep apnoea. Additionally, other organ systems or extrinsic factors may play a role *e.g.* congenital heart diseases (CHD), gastrointestinal malformations, autoimmune conditions, thyroid dysfunction, hematological disorders, and associated immunodeficiency [1 - 3]. They are also at a higher risk of pulmonary arterial hypertension (PAH) than healthy children, partly due to upper airway obstruction and CHD [4]. They are also more liable to have obstructive sleep apnea and sleep-related breathing disorders which are associated with a wide range of symptoms, including developmental delay, behavioral difficulties, impaired growth, easy tiredness and pulmonary hypertension [5]. In this chapter we will discuss the common respiratory disorders in children with DS, their etiology, prevalence, diagnosis and the possible management.

2. ETIOLOGY OF RESPIRATORY DISORDERS IN DOWN SYNDROME CHILDREN

Down syndrome is the most common chromosomal abnormalities and is related to many health medical issues. The presence of an extra copy of HSA21 chromosome in persons with DS causes over expression of about 30-50% of HSA21 genes. This up-regulation can, in turn, activate a deregulation of the expression of non-HSA21 genes. Moreover, the overdose of HSA21 microRNAs (miRNAs) may initiate down-regulation of its target genes [6]. Gene over expression has been recognized as a major influential factor for the unique DS

phenotypes. Previous genetic study had discovered a range of gene expressions accountable for many of the characteristic traits observed in DS patients including cardiovascular, brain, and gastrointestinal anomalies. However, the molecular/genetic basis underlying the pulmonary anomalies are not yet clarified enough, even though respiratory complications are the primary reason of morbidity and mortality in DS patients [7].

Dosage imbalance of genes on chromosome 21 (Hsa21) disturbs the complex gene-regulatory interactions and modifies the development to result in a wide range of phenotypes, together with the unique facial dysmorphology. Craniofacial changes may lead to wide spectrum of complications including breathing, eating, and communication problems. Proponents of the "amplified developmental instability" hypothesis argue that trisomy 21 results in a generalized genetic imbalance that disturbs evolutionarily preserved developmental pathways by diminishing developmental homeostasis and accuracy all over development. Recognition of facial prominences in the DS sample exhibiting increased changeable asymmetry during facial morphogenesis which affords an evidence for increased developmental instability in DS faces [8]. Trisomy change the expression of non-trisomic genes implicated in development leading to craniofacial structural changes associated with DS [9].The phenotypic expression of trisomy 21 generates changeable, though unique, facial morphology. Though certain facial appearance has been standardized quantitatively and qualitatively as distinctive features of DS (*e.g.* epicanthic folds, macroglossia, and hypertelorism), all of these features may present in other craniofacial disorders with a fundamental genetic etiology. Facial characters are affected in a differential way in DS, as evidenced by statistically significant variation in combination both within and between facial regions [10]. Laryngomalacia with obstruction of the upper airway is the result of increased dosage of some genes due to partial Trisomy 11q syndrome. Some genes in 11q14q25 may be responsible for laryngomalacia. A comparable effect could be observed in trisomy 21 cases that have an increased rate of laryngomalacia compared with non-syndromic children, however; studies confirmed an etiological base [11].

Human congenital pulmonary anomalies that are due to defective Sonic hedgehog (SHH) signaling comprise lung hypoplasia, tracheoesophageal fistula, tracheal

CHAPTER 6

Are Gastrointestinal Disorders of Real Concern in Children with Down Syndrome?

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Abstract: Down syndrome (DS) is a systemic disorder affecting the whole body including the gastrointestinal (GI) tract; from the oral cavity and ending with the anal canal that are involved in the food digestion absorption and excretion. These disorders could be anatomical or functional. About 10% of children born with DS have one or more forms of the structural abnormalities which may include tracheoesophageal fistula, congenital diaphragmatic hernia, small bowel obstruction, annular pancreas, and anal anomalies. Functional gastrointestinal disturbances include oral, esophageal, gastric and/or intestinal motility dysfunctions leading to feeding difficulties, prolonged feeding duration, dysphagia, gastro-oesophageal reflux disease, increased risk of aspiration, delayed gastric emptying, constipation, Hirschprung's disease and malnutrition with its effects on general health and physical compromise. These functional disturbances may be difficult to treat and may, in sequence, affect the prognosis of corrective surgeries, and hence need more cautions.

Keywords: Anal anomalies, Annular pancreas, Aspiration, Atresia, Congenital diaphragmatic hernia, Constipation, Delayed gastric emptying, Down syndrome, Duodenal stenosis, Dysphagia, Feeding difficulties, Gastroesophageal reflux disease, Gastrointestinal, Hirschprung's disease, Imperforate annus, Malnutrition, Motility dysfunctions, Small bowel obstruction, Tracheoesophageal fistula, Trisomy.

1. INTRODUCTION

Down syndrome is a systemic disorder affecting the whole body including the gastrointestinal (GI) tract which includes wide parts of the body; starting from the oral cavity and ending with the anal canal that are involved in the food

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digestion absorption and excretion. The link between gastrointestinal diseases and DS is well recognized. About 77% of neonates with DS have or will suffer gastrointestinal disorders at one time. It can cause both structural and functional abnormalities of GI tract. Children with DS are more prone to develop these disorders more than in the general population. These abnormalities can appear very early even in the early neonatal period or appear later in life in adulthood. It also can appear as serious and life threatening condition, causing immediate problems in a newborn or appear more slowly and insidious that can be missed by the parents and even the doctors. Children with DS may also develop any of the usual disorders that can be encountered by other children. Even in absence of structural and functional abnormalities of GI tract; children and adults with DS may display gastrointestinal symptoms from time to time such as vomiting, diarrhea, constipation, abdominal pain and discomfort that improve with few or no intervention much as in others. In this chapter we will shed some light on these disorders in children with DS [1].

2. STRUCTURAL ABNORMALITIES

Down syndrome is well known to be associated with gastrointestinal abnormalities and is considered as a probable predisposing state for gut anomalies and congenital heart disease as part of the VATER syndrome. About 10% of children born with DS have one or more form of the structural abnormalities which may include tracheoesophageal fistula, congenital diaphragmatic hernia, small bowel obstruction, annular pancreas, Hirschprung's disease, and anal anomalies. Esophageal atresia is noted more frequently in offspring of younger mothers and Hispanics. Hirschsprung disease is more common in boys and in infants of younger mothers and blacks, while anal stenosis/atresia is present more frequently amongst females and Asians [2]. Because of the complexity of embryonic development of the gastrointestinal (GI) tract, there is an increased risk of developmental abnormality especially in presence of chromosomal and genetic disorders including DS. These abnormalities may be structural or functional and may be complex and multiple with more than one part of the gut affected or other systems involved.

2.1. Tracheoesophageal Fistula and Atresia

Esophageal atresia and tracheoesophageal fistula (EA/TEF) are serious congenital anomalies affecting 1:3500 live births. There are five subtypes of EA/TEF have been described, based on the site of the atresia and the type of anastomosis between trachea and esophagus (Fig. **1**). Fifty percent of the patients have other associated anomalies like cardiovascular, tracheoesophageal, anal, renal, vertebral, and limb abnormalities (occurring together in the VACTERL association). DS is one of the very well studied chromosomal abnormalities that are noted in EA/TEF patients. Surgery is the best treatment; aimed to reconnect the two ends of the baby's esophagus to each other. However, in some children, a big part of the esophagus is missing so that the two ends can't be easily connected. This is known as long-gap esophageal atresia [3].

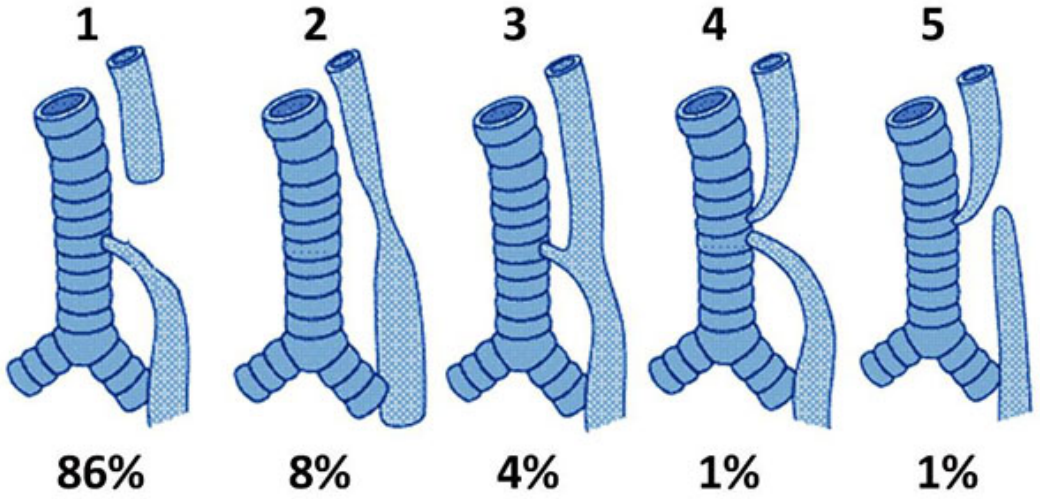

Fig. (1). Shows Different Types of Tracheoesophageal Fistula And Atresia; **1:** Atresia With Distal Fistula Which is The Most Common Type (86%), **2:** Isolated Esophageal Atresia which is The Second Most Common Type (8%), **3:** Isolated Tracheoesophageal Fistula (H type) Which is The Third Most Common Type (4%), **4:** Atresia With Double Fistula Which is a Rare Type (1%) , And **5:** Atresia With Proximal Fistula Which is a Rare Type (1%).

2.2. Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is an abnormality characterizes by presence of defective part in the diaphragm due to failure of complete closure of the diaphragmatic muscles during the fetal development in utero. Failure of

CHAPTER 7

Infection in Children with Down Syndrome

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Abstract: Infections are an important reason of increased morbidity and mortality in children with DS. Infection in children with DS characterized by increased severity of infection due to accentuated inflammatory response; increased the need for intensive care; prolonged duration of illness and need for extra or augmented treatment to cure the same infections compared with the normal population. In this chapter we will discuss the causes of increased infections in children with DS, the relation of infection to the pathogenesis of DS, the common infection in DS and immune modulation of children with DS. Every effort should be done to minimize the risk of infection and to improve their immunity.

Keywords: Air way anomalies, Antioxidants, Bacterial pneumonia, Breast feeding, Children, Congenital ear anomalies, Congenital Heart Diseases, Down syndrome, Gastro-oesophageal reflux, Hygiene, Immune aging, Immune modulation, Immunodeficiency, Infections, Nutritional deficiencies, Otitis media, Palivizumab, Pidotimod, Respiratory syncytial virus, Vaccination.

1. INTRODUCTION

Down syndrome (DS) is the most frequent chromosomal anomaly in the human being which results from incomplete or complete trisomy of the human chromosome 21. It causes various complex phenotypes which affect the whole body including the immune system. Infections are a significant reason of increased rate of sickness and death in children with DS. Infection in children with DS is characterized by increasing severity due to accentuated inflammatory response; increased the need for intensive care; prolonged duration of illness and

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the need for extra or augmented treatment to cure the same infections compared with the normal population. In this chapter we will discuss the causes of increasing infections in children with DS, the relation of infection to the pathogenesis of DS, the common infection of DS and immune modulation of children with DS [1].

2. CAUSES OF RAISED RATE AND SEVERITY OF INFECTIONS IN DS CHILDREN

The raised rate of infection in DS children is due to different factors. Immune deficiency increases both frequency of infection and the severity of associated inflammation. Anatomical co-morbidities are important factors that could precipitate infections or exaggerate its severity.

There are different airways anatomical abnormalities, congenital ear abnormalities, increased prevalence of gastroesophageal reflux disease (GERD), muscular hypotonia, and increased incidence of congenital heart disease.

Nutritional deficiencies may be another factor in areas where adequate care is not available to this cohort of patients. Children with DS may have also a poor vaccination response.

2.1. Immunodeficiency in Children with Down Syndrome

The immune system plays an essential but complex role to protect against infections with different microbes. It also controls the degree of inflammation that results from these infections.

Without adequate immune status, recurrent or life threatening infections are inevitable and severe inflammatory response with undesirable tissue damage may be triggered in response to infections. Relative immunodeficiency is commonly underestimated in children with DS that could place those patients at great risk (Fig. **1**).

2.1.1. Genetic Basis of Immunodeficiency in Down Syndrome

Partial or complete triplication of chromosome 21 may be associated with gene

over expression which could be responsible for many disturbances in the immune system of patients with DS.

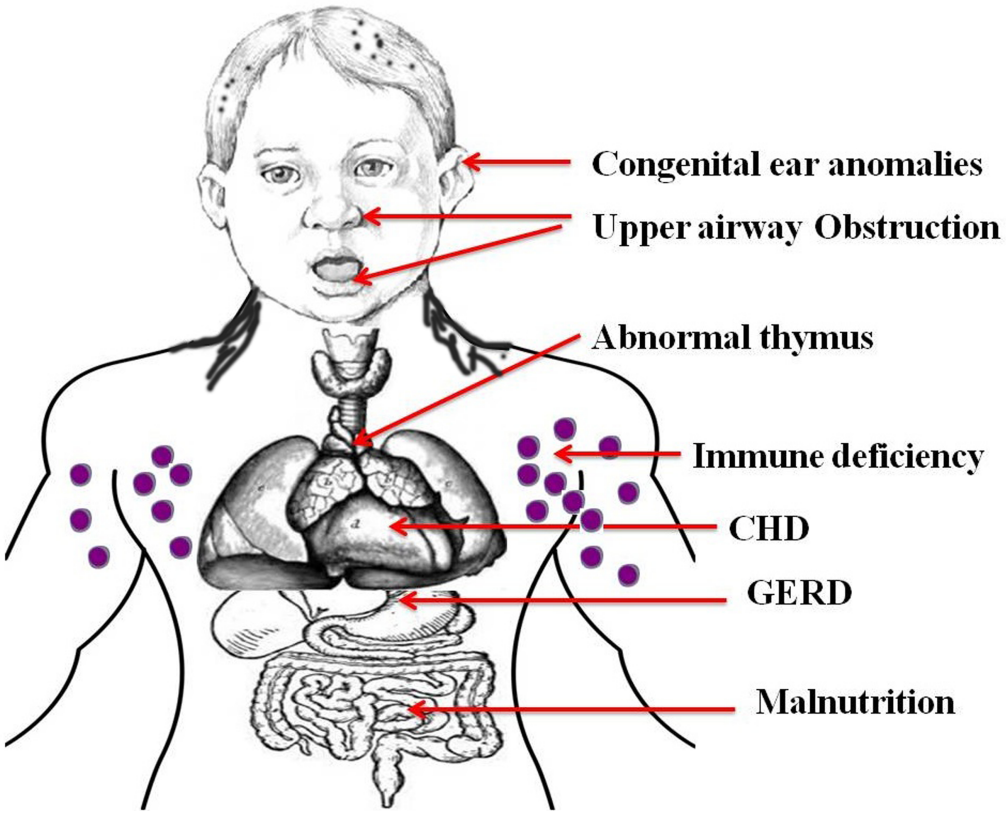

Fig. (1). Showed causes of immune deficiency in children with down syndrome.

Chromosome 21 has a 21q22 gene-rich R bands which called the "Down syndrome region and contains about 225 genes. Among these genes; many genes encode for many proteins responsible for the proper functioning of the immune system. Among these are the genes that encode for CuZn-superoxide dismutase (SOD-1), the regulator of calcineurin 1 (RCAN1), CD18-beta chain of LFA-1, interferon receptor, APP-amyloid precursor protein, and protein S-100 beta. RCAN1 is a transcription factor that depresses the signal transduction provoked by the nuclear factor of activated T cells (NFAT), and has been found to decrease the inflammatory responses in mice by maintaining an inhibitor of nuclear factor-

CHAPTER 8

Update in Hematology and Oncology in Down Syndrome

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Abstract: Down syndrome (DS) is commonly associated with hematological and oncologic disorders than non-syndromic children. Interpretation of the blood picture should be done with caution. Polycythemia and iron deficiency anemia (IDA); both are common in those children. Presence of IDA in DS children adds an extra load on them. Occurrence of transient abnormal myelopoiesis (TAM) in DS neonates is due to the effect of trisomy 21 on liver hematopoiesis with megakaryocyte – erythroid progenitor. Down syndrome children have a 500- fold increase in acute myeloblastic leukemia (AMKL) compared to the non-syndromic children. They also have increased risk for development of acute lymphoblastic leukemia (ALL) which affects 1 in 300 children with DS. At the same time; despite the high prevalence of leukemia's in DS children; the risk for the development of solid tumors is globally unexpected to be low. Several novel therapies will benefit many children with DS and ALL and other malignancies.

Keywords: Anemia, Angiogenesis-promoting protein vascular endothelial growth factor, Antigen-directed immune therapies, Blood picture, Children, Down syndrome, DSCR1, Hematological abnormalities, Iron deficiency, Leukemia, Liposomal formulations, Lymphoblastic, Myelodyplastic syndrome, Myeloid, Nephroblastoma, Neuroblastoma, Neutropenia, Polycythemia, Ruxolitinib, Transient abnormal Myelopoiesis.

1. INTRODUCTION

Hematological disorders are more common in children with Down syndrome (DS) than non-syndromic children. Evaluation and interpretation of blood picture in individuals with DS may need caution as it can cause some confusion. The blood cell counts (CBC) may reflect some abnormalities without an apparent reason as

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well as the base lines of different parameters in the complete blood count may differ from the normal population. Some of these abnormalities resolve spontaneously and others persist throughout life. Such hematological abnormalities as increased mean corpuscular volume (MCV) can make the diagnosis of iron deficiency anemia difficult. Other abnormalities may include mild transient neutropenia, thrombocytopenia or thrombocytosis, as well as increased counts of circulating nucleated red cells with or without polycythemia [1]. At the same time; the risk of the development of acute lymphoblastic leukemia (ALL) increases up to 12 times in the age group between 5 years and 30 years and increases up to 40 times in children less than 5 years. The risk of the development of acute myeloid leukemia (AML) increases up to 150 times in children less than 5 years [2].

2. COMMON HEMATOLOGICAL ABNORMALITIES IN DS CHILDREN

2.1. Polycythemia

Sixty five percent of newborns with DS are presented by polycythemia which may or may not be associated with congenital heart diseases. This type of polycythemia is frequently not in need for treatment because of spontaneous resolution within few months. The treatment is limited to those with hyperviscosity syndrome. The development of polycythemia may be due to the increased erythropoietin levels in the setting of chronic intrauterine hypoxia. On the contrary, children with DS may present with iron deficiency anemia due to decrease dietary intake of iron because of delayed motor skills, hypotonia and dysphagia [2, 3].

2.2. Iron Deficiency Anemia (IDA)

There are few studies regarding IDA in DS. Children with DS have been associated with motor and cognitive developmental deficits. The presence of IDA in those children add an extra load on them, so screening for IDA is mandatory [4, 5]. The diagnosis of IDA in children is faced by the difficulty in screening of these children. Mean corpuscular volume (MCV) is usually high in children with DS, which is not related to Vitamin B12 or folic acid deficiencies [6]. Many researchers have documented erythrocyte macrocytosis in DS adults and children.

However; its clinical significance is still unclear. The explanation of macrocytosis could be that it is not a reflection of reduced red cell survival but may be related to altered folate remethylation pathway, secondary to increased cystathionine β-synthase (CBS) activity which is controlled by a gene present on chromosome 21 [7] As a result, macrocytosis makes characterization of IDA more difficult. This should be considered during evaluation of iron status of children with DS which should be monitored by both serial complete blood counts (CBCs) and iron studies with special emphasis upon serum ferritin.

2.3. Transient Abnormal Myelopoiesis (TAM)

The true incidence of transient abnormal myelopoiesis in DS is not actually known. Ten percent of neonates with DS are affected and about 10% of the fetuses may die intra uterine mostly due to TAM [7, 8]. The development of TAM in DS may be due to the effect of trisomy 21 on liver hematopoiesis together with megakaryocyte – erythroid progenitor frequency with common myeloid progenitor [7].

There are variable clinical presentations of TAM among the different cases with DS; where most cases are picked up during the routine testing by presence of circulating blast cells with or without leukocytosis [9]. Other cases may present with bleeding tendency, organ affections as, respiratory distress, hepatic dysfunction and/or pericardial effusion. Majority of TAM cases usually recover spontaneously within 3 months but, about 20-30% will develop acute myeloid leukemia of DS (ML-DS) [10, 11].

The diagnosis of TAM depends on the clinical manifestations and the presence of characteristic findings in the peripheral blood film; as nucleated red blood cell, thrombocytopenia or thrombocytosis, giant platelet and fragments of megakaryocyte with the characteristic basophilic immature blast cell. Blast cell in TAM undergo flow-cytometry express unique markers; as early myeloid (CD34, CD33), megakaryocyte (CD41, CD61), and erythroid (CD235a, glycophorin) markers (2). The differentiation between TAM and true AML is difficult, but TAM has usually a spontaneous resolving course. All neonates with DS and apparent leukemia who are well should initially be monitored for possible

CHAPTER 9

Neurological Manifestations of Down Syndrome

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Abstract: Down syndrome is the most common chromosomal abnormality. A variety of neurological manifestations including stroke, epilepsy, cervical spinal cord compression, and basal ganglia damage may complicate the syndrome. As the neurologists have little chance to see a good number of DS patients and hence their expertise in this field is lesser than psychiatrists, it is suggested that cooperation between both neurologists and psychiatrists especially the learning disability might lead to better outcome of neurological complications of DS. This chapter reviews the commonest neurological complications associated with DS.

Keywords: Alzheimer disease, Antiphospholipid antibodies, Atlanto-axial subluxation, Cerebral infarction, Cervical spinal cord compression, Children, Cognitive functions, Dementia, Down syndrome, EEG, Epilepsy, GABAergic transmission, Hypotonia, Intellectual disability, Memory, Mental retardation, Moyamoya disease, Pronoun comprehension, Protein C deficiency, Stroke, Trisomy 21.

1. INTRODUCTION

Trisomy 21 or Down syndrome (DS), is the most common chromosomal defect, its incidence in the United States is 1/733 live births [1]. In 1866 the British physician, John Langdon Down had described the condition of DS for the first time in a clinical lecture report entitled "Observation on the ethnic classification of Mongoloid idiots" [2]. Down syndrome has manifestations in many systems and is one of the major reasons for mental retardation. A variety of neurological manifestations including stroke, epilepsy, cervical spinal cord compression, and basal ganglia damage may complicate the syndrome [3]. All patients with DS

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eventually develop neuropathologically Alzheimer's disease-like findings, and sometimes clinically associated with dementia [4, 5]. Diagnosis of epilepsy was confirmed in seven only cases in more than 4500 (0.2%) general referral of patients with DS suspected to have seizure disorders seen in neurology outpatient clinic by a consultant neurologist over a five-year period. Only one new, comorbid, diagnosis was made. Neurologists have little exposure to, and hence little chance to develop expertise in, the neurological complications of DS [6].

2. NEURO-ANATOMIC FUNCTIONS OF THE BRAIN IN DOWN SYNDROME

2.1. Gross Anatomy

Even when the measure is corrected for reduced body size, the brains of adults with DS are about 20% smaller than typically developing brains [7]. Brain changes, still incompletely understood, and fall into 2 categories. The first is a subtle developmental abnormality that results in lifelong mental retardation. The second is a less subtle, almost absolute predisposition to severe Alzheimer disease that commences at relatively young ages (forties, or even thirties) and results in demonstrable cognitive decline in these already impaired individuals [8]. Brains from DS patients are smaller than normal, often around 1,000 g in weight, with corresponding reductions in neuronal content. They show a characteristic rounding of contour and shortening in the anterior-posterior axis with a steeply rising, almost vertical occipital outline. A small superior temporal gyrus is also characteristic and the cerebellum and brainstem are also often disproportionately small. Subtle abnormalities such as focal heterotopias, polymicrogyria, and other abnormal convolutional patterns may also be found [9, 10]. All brain structures except for the parahippocampal gyrus are smaller in DS patients than in controls. The lateral and the third ventricles are larger in DS patients. Significant (non-zero) occipital petalia are found only among DS subjects. The volume of the frontal tips is larger in the right hemisphere in 69% of DS subjects and in 92% of controls. The volume of the occipital poles is greater on the left in 77% of DS subjects and in only 50% of controls. None of the group differences in petalia are significant. There is no relationship between the presence of petalia and handedness, and removal of left-handed subjects does not alter the results. Among

the DS subjects, the age-related pyramis shrinkage is accompanied by reduction of the volumes of the cerebellar hemispheres and the caudate [11].

2.2. Microscopic Study

The most striking finding in young DS brains is apparent only with special Golgi preparations. Neuronal dendritic trees are normal in DS fetuses, but these fail to show the progressive increase in dendritic number and complexity that is seen in normal individuals from birth to young adulthood. This results in a striking "tree in winter" appearance of neuronal dendrites that persists into adulthood, and that immediately suggests a morphological substrate for mental retardation [12, 13]. In four old DS females with a mean age of 69 year, the total number of neurons and glial cells in the mediodorsal thalamic (MDT) nucleus was estimated and compared to six age- and sex-matched controls. Using the optical fractionator technique, The MDT nucleus was delineated on coronal sections, and cell numbers (large and small neurons, oligodendrocytes, and astrocytes) were estimated. The total neurons in the MDT nucleus in brains of the DS women was significantly lower compared with controls; 3.41×106 in DS and 5.97×106 in the controls, with no overlap (2p=0.004), large (projecting) and small (local inhibitory) neurons nearly affected equally. On the other hand, there were no significant difference in glial cell population of DS brains compared with controls. The basal ganglia were unaffected while the cortical structures of the same four DS brains were estimated to be half the normal size of controls with a reduction in cell numbers. The exact cause of reduced number of cells in MDT nucleus could not be determined but developmental delay, premature aging, and Alzheimer-like pathology could provide an evidence for a local reduction in neuron numbers in the MDT nucleus, which could affect the cognitive capacity of patients with DS [14].

2.3. Structural and Functional Neuroimaging

Early structural MRI reports suggested that total intracranial volume is smaller in DS, with the greatest volumetric differences in the cerebellum, brainstem, and frontal lobes [15]. Hippocampal volumes have been found to be smaller than for typically developing individuals [16]. A voxel-based morphometric analysis

CHAPTER 10

Psychological Change in Down Syndrome Children and Adolescents

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Abstract: Children and adolescents with DS are exposed to significant physical, sexual and emotional developmental changes. They also often have some psychiatric problems as externalizing disorders, depression, anxiety and/or obsessive-compulsive disorder.

They also suffer from behavior and psychosocial problems in the process of their growth, such as expressing their feelings, learning problems as their shortage of language and cognition. Children with DS are amenable for good education and they can enter a special education school for special education, so that training of their fine motor, gross motor and intellectual abilities is helpful to improve their development.

They can be encouraged to improve body functions and accentuating gaining more functional proficiencies that facilitate improving participation in age-suitable activities. Early detection and proper treatment of emotional, psychiatric or developmental disorders ensure good prognosis.

Keywords: Abuse, Academic achievements, Anxiety, Articulation, Behavioral, Children, Communication, Depression, Developmental, Down syndrome, Education, Early Stimulation Emotional, Grammar, Mental, Obsessive-compulsive disorder, Phenotypes, Psychological, Sexual, Speech, Talking.

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1. INTRODUCTION

In general, adolescence stage is defined by quick change from dependence to independence. They start to feel their need for being somewhat free in travelling; running money, choosing friends and freedom interests, looking out their personal daily needs. They start to prepare themselves to leave the family home by 18 years of age. This period shows also significant physical, sexual and emotional developmental changes. The same changes are also observed in children and adolescents with Down syndrome (DS); when they show considerable growth in all era of development during their adolescence and into early adult life. They behave in an essentially similar way to other teenagers and should be recognized as such. They keep on developing their fundamental abilities and experiences in speech, language, literacy and numeracy and teaching process. They commonly demonstrate psychiatric problems as externalizing disorders, depression, anxiety and obsessive-compulsive disorder. They suffer also from behavior and psychosocial problems in the process of their growth, such as expressing their feelings, learning problems as their shortage of language and cognition. These issues are reflected on the concepts of academic achievement, psychosocial stress emotional challenges, behavioral disorders, communication disorders and development of autism. All problems above will be aggravated by negative behaviors and emotion of parents or others and also evoked by some strange things such as moving house. Understanding social development in this category of children will help to develop effective interventions and teaching strategies [1].

2. MENTAL DEVELOPMENT

Down syndrome is the main genetic reason of mental retardation and patients with DS demonstrate marked psychopathologic changes (18-23%). Over expression of genes present on chromosome 21 induces change in biological stability state in the DS brain to a new less functional condition causing variable degrees of mental retardation. The expression variability caused by this gene-dosage imbalance may initially stimulate brain functional variability at cellular level, as primary phenotypes, and lastly stimulate neuromorphological changes and cognitive deficits as resultant phenotypes. Identification of over expressed trisomic genes in the brain and their function, their over expression-induced effects on regulation of

neurological development, their downstream effects, their interaction with other proteins, and their role in regulatory and metabolic pathways is providing us with a clearer vision about the origin of the mental retardation (MR) in DS. Children with DS have a delayed and sub mental development (Oligophrenia) as a cardinal sign of the syndrome with a variable degree of mental retardation from mild to profound. Their Intelligence Quotient (IQ) is usually between 25 and 50 with more gaps between them and their peers and their IQ will go lower with advancing age. This difference in IQ level is mainly due to heterogeneity of phenotyping. The low IQ observed in DS is recognized by delay in development, impaired language skills, deficits in memory and other cognitive function abnormalities. Individuals with mosaic forms of DS have been found to score 10–30 points higher on IQ measures than those with trisomy 21, and have demonstrated normal visual perceptual skills. Language development is often delayed or impaired in people with DS; they understand more than they can verbalize [2]. They also show a decrease of cognitive functions related to ageing and is characterized by declining in memory, language and other cognitive functions. The linguistic development in DS progresses differently along unique developmental trajectories. Thus, for example, morphosyntax defects, especially in production, is more obvious in adolescence than in early childhood and lexicon is usually better conserved in all ages (at least in comprehension) [3, 4].

They are usually able to sit after one full year of life, and sometimes walking will be delayed till the age of 3 years. Children with higher IQ can learn to read and to do simple manual work while children with lower IQ will have more difficulty in language and self-reliance. However, training can improve their abilities to do more work regardless of their sub-mental abilities. This sub mental development observed in DS is related to occurrence of errors in neurodevelopment during fetal stage of the central nervous system (CNS) development. There is reduction in the total number of neurons throughout several cortical areas, abnormalities within the neurons themselves, and abnormalities in the ability of the neurons to communicate with each other with reduction in the neuronal density in cortical areas and decreased dendritic arborization. The cerebral cortex is the most affected area of the brain. Reduction in the number of neurons, existence of dendritic spines, and poor synaptic connections contribute to difficulties in

CHAPTER 11

Anesthesia in Down Syndrome Children

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Abstract: Down syndrome (DS) Children are more liable for frequent sedation and anesthesia either for imaging procedure or for surgical intervention. They have many risk factors that increase the anesthesia related complications. These risk factors include cardiac, esophageal, gastrointestinal or urinary tracts, eyes, ears, and joints anomalies. There is also an increased risk of infection due to immune deficiency. Proper preoperative, operative and post operative management are mandatory to decrease the anesthesia-related complications. In this chapter; these co morbidities and the factors that increase the risk of complications during anesthesia will be addressed, as well as pre-operative, intraoperative and post-operative management will be discussed.

Keywords: Anesthesia, Atropine, Cardiac, Children, Cognitive, Down syndrome, Ears, Epilepsy, Esophageal, Eyes, Gastrointestinal, joints anomalies, Mental retardation, Operative, Post operative, Preoperative, Sedation, Sleep apnea, Trisomy, Urinary tracts.

1. INTRODUCTION

Sedation and anesthesia are frequently needed for children with Down syndrome (DS); either for imaging procedure or for surgical intervention. Infants and children with DS have more frequent congenital anomalies than non-syndromic children. About 50% of these children have major cardiac anomalies that may require early surgical intervention. Other major anomalies that may involve esophageal, gastrointestinal or urinary tracts, eyes, ears, and joints may also need early intervention. Proper sedation and anesthesia are needed to carry on with imaging and surgical correction of these anomalies [1]. Anesthetic care for

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children with DS may be a real challenge even for the most well experienced anesthesiologist. This challenge arises from the increased frequency of numerous functional co-morbidities that are frequently encountered in these children. These co morbidities can affect any system and organ ranging from unnoticed condition *e.g.* hypersensitivity to atropine; to a serious medical problem *e.g.* complex congenital heart diseases. These augmented with the characteristics emotional, psychological and mental problems of children with DS and their inability to recognize their sickness increase the difficulties that meet the anesthesiologist when dealing with them and conducting preoperative risk evaluation, perioperative management, and maintenance of their vital organ functions. During sedation or anesthesia; they are more liable to have difficult airways, altered respiratory mechanics, problems related to gastric reflux, cardiovascular compromise and neuromuscular disorders. Knowledge of these frequent disorders can assist anesthesiologist to arrange safer practice in DS people.

2. ASSOCIATED CO MORBIDITIES THAT COULD INCREASE ANESTHESIA RISKS AND COMPLICATIONS

2.1. Cognitive, Cerebral and Neurologic Problems in DS children

Neurological disorders in children with DS are relatively common. These disorders could be anatomical or functional including disordered neurotransmission. People with DS have structural abnormalities in the nerve cells including the neuronal axis, cerebellum and central structures with alterations of the neurotransmission system, and vulnerability of the cholinergic and noradrenergic systems [2]. They have decreased pain perception due to the raised levels of opioid peptides in the frontal cortex of these people which explains the increased pain threshold in DS patients. Peripheral somatosensory hypofunction including transmission of painful stimuli is another cause of decreased pain perception. This altered pain tolerance, and the incapacity to give a qualitative and quantitative pain description cause difficulty in measuring pain in children with DS [3]. Variable degrees of mild to moderate mental retardation (IQ between 20 and 70) with inadequate understanding in contrast to the normal children of similar age in addition to severe learning difficulties; are observed in these children. Many of them may have lack of cooperation due to fear, anxiety, and

incapacity to communicate rather than due to the degree of mental retardation. They also may show a tendency towards hyperactivity [4].

Children with DS have impaired expressive communication capabilities, but they have relatively more developed receptive communication skills. Thus, they can feel the nervousness and anxiety in their caregivers, and will respond to what they feel. Expressive language development is often delayed or impaired in children with DS as they understand more than they can verbalize. Proper communication is essential for comfortable transition of the patients into unfamiliar environments or scenarios. Difficult communication observed in children with DS may increase their anxiety & agitation before anesthesia and they may have some difficulties describing pain & other symptoms. Yoshikawa *et al*. found that the risk of hypoxemia and delayed recovery after midazolam administration is increased in children with DS, or mental retardation. Patients with mental retardation may show vigorous treatment-refusal actions. Anxiety & agitation can lead to unsafe behavior and possible injuries to patient, family, or health care providers. They may have marked sympathetic nervous system stimulation and possible "fight or flight" body reaction that may take part in anesthetic complications [5]. Lack of adequate communication impairs the ability of children with DS to describe their feelings with pain, nausea and other symptoms that may have. This may increases the risk of misdiagnosis of anesthesia related complications and hence inadequate treatment [6].

Epilepsy can occur in 5-10% of children with DS. These children are at increased risk of missing scheduled anticonvulsants during the home-to-hospital transition, including when being admitted for procedures requiring anesthesia. This may contribute to breakthrough seizures because of lowered anticonvulsant levels [7]. At the same time; epileptic seizures can occur during anesthesia. Some of the used general anesthesia medication can induce epilepsy as sevoflurane and enflurane. Sevoflurane is considered as the gold standard for inhalation induction anesthesia in children. Nevertheless; high concentrations of sevoflurane can induce epileptiform electroencephalographic signs in both children and adults in the form of polymorphic spike-wave, polyspike-wave and periodic epileptiform discharges that come before electroencephalographic or actual clinical seizure [8]. Enflurane is also able to provoke seizures and is used to stimulate epileptic foci during

CHAPTER 12

Dental Problems in Down Syndrome Children

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Abstract: Down syndrome (DS) is a common malformation affecting the whole body with a unique craniofacial and distinctive oral feature and anomalies. These dental anomalies and the associated systemic manifestations of children with DS pose real challenges to the dentist as well as the pediatrician which necessitate a multidisciplinary team to be involved in taking care of children with this syndrome. It is important that the dentist can recognize the types of structural soft tissue and dental abnormalities which are part of the classic features and developmental prototype of D children. The dentist should also be able to detect and to appropriately manage these problems through an integrated team work including the family and the child primary physician. Good oral hygiene and healthy dental life are of paramount importance for an integrated health and better quality of life for such children.

Keywords: Anodontia, Bruxism, Children, Craniofacial, Down syndrome, Gingiva, Gingivitis, Halitosis, Hypotonia, Oral health, Occlusion, Oligodontia, Palate, Periodontitis, Periodontal disease, Taurodontism, Teeth, Tongue, Tracheoesophageal fistula, Tooth agenesis.

1. INTRODUCTION

Down's syndrome (which is also known as trisomy 21, trisomy G, and mongolism) is a systemic disorder occurs as a result of genetic alteration due to triplication of human autosomal chromosome 21 with a frequency of 1/800-1000 live births in different populations. It is the commonest of all malformation

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syndromes that affect human beings [1]. It has certain characteristics that affect the whole body including generalized hypotonia, mental retardation, and unique craniofacial and distinctive oral features, regardless of race or ethnicity. Both the dental anomalies and the associated systemic manifestations of children with DS pose real challenges to the dentist as well as the pediatrician which necessitate a multidisciplinary team to be involved in taking care of these children. It is important that the dentist can recognize the types of structural soft tissue and dental abnormalities which are part of the classic features and developmental prototype of D children. An Oral Health Care provider should be aware of all the underlying medical conditions of his patient, the complications that he/she can come across in future, and what precautions one should take to avoid any adverse events in the clinic. Understanding patients' medical condition helps the dentist to start preventive measures early. However, professional care alone is not sufficient enough for good and adequate oral health; support from the parents and (primary) care-givers is of crucial importance [2]. In this chapter; we will discuss the oro-cranial changes, the patho-mechanism, the magnitude and the types of dental problems in children with DS (teeth, gingiva, tongue, palate and occlusion). Clinical significance and management of Dental problems in children with DS as well as proper home care and prevention of these problems will be discussed.

2. CRANIO-FACIAL CHANGES IN CHILDREN WITH DS

Several oro-facial features are characteristic of people with DS. These changes could affect both hard tissues and soft tissues and can affect feeding, chewing, swallowing, and speech.

2.1. Hard Tissues Changes

These features include an overall reduction in head size, short neck together with a modification of head shape; and a relatively concave facial profile. There is a decrease in the interorbital distance, small palpebral fissures, upper slanting of the eyes with epicanthic folds, ocular hypotelorism, strabismus and prominent forehead [3]. With the reduced head size of children with DS, there is also lesser brain size than non-syndromic children with diminution of parietal cortex, and the temporal lobe which occur as a result of improper neural development associated

with DS [4]. The mid-facial zone may be less developed, impacting the look of the lips, tongue and palate. There is also hypoplasia of the middle third of the face with poorly developed paranasal air sinuses, with depressed nasal bridge; decreased nasal protrusion, small nose producing an inclined forehead and a flat face with smaller ears. Maxillary development is deficient in vertical height which induces over closure of the mandible and thus protruding the lower arch anteriorly comparative to the upper [5].

The lower third of the face is also reduced with mandibular prognathism. The mandible is smaller (micrognathia) than non-syndromic children. The maxilla, the nasal bridge, and the mid-face bones are less developed than in the normal population, inducing a prognathic occlusal relation, small oral cavity and broader alveolar ridges. The palate, though being of average size, may seem highly arched and narrow. This misleading look is due to the abnormal thickening of the sides of the hard palate. This thickness limits the space amount the tongue can take up in the mouth and influences the capability to talk and chew. Underdevelopment of the mid-face reduces the size and deepness of the palate [6].

There is reduction of the anterior skull base and anterior-posterior cranial base lengths are shorter with a backward inclination of the posterior cranial base in DS children than non syndromic children that cause protrusion and proclination of lower incisors and class III malocclusion. There is also hypoplasia of maxilla and mandible with a retrognathic maxilla and shorter effective length, and increased lower facial height with an increment in the mandibular plane angle, smaller mandibular ramus and body, a tendency to skeletal open bite and a hyperdivergent mandible. Bimaxillary dental protrusion may present in DS children with prominent lips and a reduced nasolabial angle [7].

There are controversial data about the palatal morphology in children with DS. The palate is frequently described as high-arched with narrow palatal vault. Other findings suggest that the palate in DS subjects is generally smaller. Objective evaluation confirmed that the palatals vault in DS is smaller than in normal subjects. The palatal dimensions in DS are in lower depth, and shorter in height. Early hypotonia in DS and lingual diastasis were recognized as an etiological factor of specific palatal morphology with soft tissue prominence along the palatal

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