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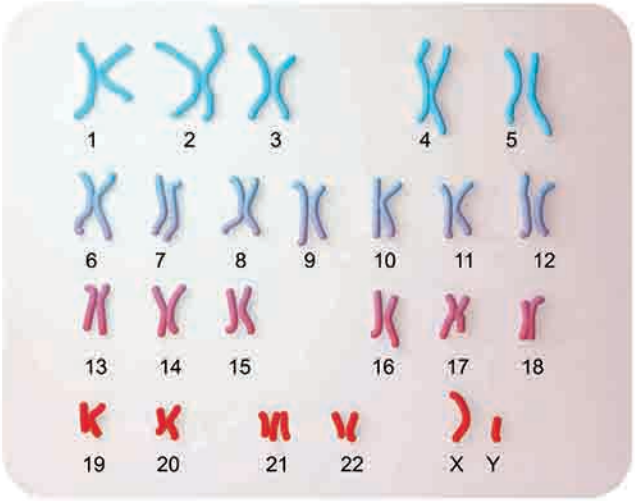
IAP *Textbook of* DOWN SYNDROME



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Contents

SECTION 1: GENERAL CONSIDERATION

1. **History of Trisomy 21** 3
   Shaji Thomas John
2. **Chromosomal Basis of Trisomy 21 and Genetic Counseling** 8
   Sheela Nampoothiri
3. **Prenatal Diagnosis and Genetic Testing for Down Syndrome** 13
   Selvamanojkumar S, Neerja Gupta
4. **Down Syndrome: Clinical Features** 18
   Mohandas Nair Karippoth
5. **Development Aspects in Down Syndrome** 21
   Riya Lukose

SECTION 2: SYSTEMIC MANIFESTATIONS

6. **Congenital Heart Disease in Down Syndrome: Special Considerations** 29
   Sonia Karapurkar, Balu Vaidyanathan, Krishna Kumar R
7. **Endocrine Problems in Children with Down Syndrome** 37
   Menon PSN, Vijayakumar M
8. **Growth Monitoring** 46
   Riya Lukose
9. **Musculoskeletal Issues in Down Syndrome: A Guide for Pediatricians** 50
   Easwar T Ramani
10. **Hematological Abnormalities in Children with Down Syndrome** 59
    Sankar VH
11. **Renal and Urinary Tract Abnormalities** 62
    Gayathri K
12. **Gastrointestinal Manifestations of Down Syndrome** 65
    Riyaz Arakkal
13. **Dermatological Manifestations in Down Syndrome** 69
    Abhay Mani Martin
14. **Dental Care in Persons with Down Syndrome** 72
    Nidhi Gupta, Anurag Gupta
15. **Down Syndrome and the Eye—Significance of Early Screening** 78
    Leila Mohan

16. **Down Syndrome: Otolaryngological Manifestations** 84
Manoj MP

17. **Puberty, Sexuality, and Management of Menstrual Cycles** 91
Gayathri K

18. **Neuropsychiatric and Behavior Disorders in Children with Down Syndrome** 94
Krishnakumar P

SECTION 3: DEVELOPMENTAL THERAPIES

19. **Early Intervention in Children with Down Syndrome** 101
Muhlisa V

20. **Down Syndrome: A Psychological Perspective** 109
KS Mohan, Sharada Mohan

21. **Enhancing Communication in Children with Down Syndrome: Recent Advances in Intervention** 112
Neethu Koroth, Sreerenthu S Viswan, Fayeda TK, Rasitha Harish

SECTION 4: DEFINITIVE COUNSELING AND INCLUSION

22. **Counseling: Antenatal to Vocational** 119
Shaji Thomas John, Gayathri K

23. **Vocational Training and Placement for Persons with Down Syndrome** 123
Jayaraj MK

24. **Community-based Rehabilitation for Neurodevelopmental Disorders** 129
Krishnakumar P

SECTION 5: LEGAL ASPECTS AND THE FUTURE

25. **Controversies in Management of Down Syndrome** 135
Shaji Thomas John

26. **Legal Aspects and Decision Making** 138
Shaji Thomas John

27. **The Road Ahead** 142
Shaji Thomas John

28. **Success Stories** 147
Shaji Thomas John

Epilogue *153*

Index *155*

CHAPTER 7

Endocrine Problems in Children with Down Syndrome

Menon PSN, Vijayakumar M

JAYPEE BROTHERS

INTRODUCTION

Endocrine problems are common in children with Down syndrome (DS), and their reported incidence is much higher than in the general population. These include thyroid dysfunction, short stature, gonadal dysfunction, infertility, decreased bone mass, vitamin D deficiency, propensity to overweight/obesity, and diabetes mellitus. The prevalence increases as age advances. Precise diagnostic criteria and effective management protocols do exist for some endocrine comorbidities of DS in most developed countries; however, consensus on the best clinical practice recommendations has not yet evolved for many comorbidities of DS, especially in low- and middle-income resource countries. The recent recommendations by the Indian Academy of Pediatrics (IAP) for DS children are a welcome step in this direction.

THYROID DISORDERS

Thyroid dysfunction is the most common endocrine malfunction noted in children with DS, with an earlier onset, and it is often transient. It is not related to the gender of the child, weight, and associated comorbidities. The prevalence of thyroid disorders is much more common in DS compared to the general population. Various prevalence rates ranging from 3 to 54% have been reported in children with DS in combined pediatric age groups, with a lifetime prevalence of 13–63%. A 10-year prospective Italian study reported the probability of developing hypothyroidism increasing from 7 to 24% at 10 years. The risk for the development of thyroid dysfunction increases by 10% annually, with a significant increase in transient forms. There are a few studies from various parts of India, in which hypothyroidism was noted in 13.6–31.2%, with no difference among various cytogenetic groups of DS in some. Both hypothyroidism and hyperthyroidism are described, but hypothyroidism is much more common and includes congenital and acquired thyroid disorders.

Congenital Hypothyroidism

Congenital hypothyroidism (CH) is reported to be 28–30 times more common in neonates with DS. It is seen in approximately 1% of neonates with DS, and 50% of these newborns show altered thyroid function characterized by low free thyroxine (FT4) and elevated thyroid-stimulating hormone (TSH) levels. A review of published literature showed the incidence of primary CH to be 1 in 113–141 livebirths in DS compared to 1 in 2,000–3,000 livebirths in the general population.

Some cases of CH with DS are missed on routine newborn thyroid screening programs and picked up on thyroid tests performed within the first 6 months of life. The American Academy of Pediatrics (AAP) recommends screening for CH in all newborns, and the screening test has to be repeated at 6 months, 1 year, and every year thereafter in children with DS. Many developing countries follow similar screening guidelines. There are no specific Indian guidelines for newborn thyroid screening in DS, and the general guidelines for newborns are followed. The frequency of testing needs to be increased in those with subclinical hypothyroidism (SCH). Some experts recommend an additional screen for thyroid diseases between the newborn period and 6 months of age in children (preferably at 3 months) for early detection of CH missed during newborn screening. The justification for this recommendation is that CH is an evolving disease, and many infants who were reported to be normal during newborn screening may develop CH earlier than 6 months of age, with disastrous consequences in psychomotor development.

The TSH and FT4 cut-offs used for screening CH in children with DS are the same as those for normal children. A retrospective study of 159 newborns with DS demonstrated that T4-based newborn screening may miss cases of CH, and a combined FT4 and TSH screening is preferred. The current evidence suggests

an annual increase of thyroid abnormalities by 10% and transient dysfunction in about 13%. Despite these recommendations, many children with DS are missed during newborn screening for CH and are detected at a later age.

Subclinical Hypothyroidism

The incidence of SCH characterized by elevated serum TSH and normal FT4 is higher in children with DS, and this is likely to be missed in T4-based screening programs. It is reported in 25–32% children with DS. SCH is usually asymptomatic in DS and tends to be transient and self-limiting. Almost 50% of children with SCH in DS have antithyroid antibodies, and half of these may progress to overt hypothyroidism on follow-up. Nonautoimmune SCH is more common and occurs earlier than autoimmune thyroiditis in DS, indicating a probable role of the chromosomal alteration in the onset of thyroid dysfunction.

The clinical significance of SCH in DS and the need for treatment is a matter of debate. Mild improvement in motor development and height has been reported with early treatment, but follow-up at 10 years found no developmental differences in different groups in a single-center, double-blinded, randomized controlled trial. The available evidence suggests that SCH with persistent elevation of TSH levels >10 mU/mL coupled with a goiter, or presence of antithyroid antibodies, requires treatment with thyroxine, proper follow-up, and dose titration. There is a progressive deterioration of thyroid function over time as children grow up as adolescents and adults, further increasing the prevalence in long-term studies. This has been noted in children with DS in association with higher baseline TSH levels and those with autoimmunity.

Transient Hypothyroidism

The incidence of transient hypothyroidism is also higher; many of these children are likely to be off therapy by 3 years. The high frequency of TSH elevation in DS probably suggests a resetting of the hypothalamic-pituitary-thyroid axis rather than true SCH. In view of the relatively high incidence of transient hypothyroidism, trials off levothyroxine may be considered in both congenital and transient hypothyroidism, especially if the TSH elevation is mild (<10 mU/mL), and treatment with levothyroxine is recommended only if clinical symptoms are present or TSH elevation (>10 mU/mL) persists.

Etiology and Pathogenesis of Congenital Hypothyroidism

The etiology of CH does not seem to be thyroid agenesis, as most DS patients have no abnormalities in thyroid scans. Reported causes of CH are thyroid hypoplasia, thyroid ectopia, or partial agenesis.

The reasons for increase in prevalence of CH in children with DS are the following:

- Delayed maturation of the hypothalamic-pituitary-thyroid axis leading to a higher TSH level with normal FT4 and FT3 levels
- Peripheral resistance to thyroid hormones leading to inappropriate TSH secretion and release, probably of a central etiology
- TSH insensitivity and reduced TSH bioactivity

Recent studies have suggested a probable role of increased oxidative stress in patients with DS and thyroid dysfunction. The role of elements such as copper, zinc and selenium as well as enzymes such as superoxide dismutase (SOD1), phenylalanine hydroxylase, and dual specificity tyrosine-phosphorylase-regulated kinase 1 (DYRK1A) in the development of thyroid dysfunction is under evaluation.

Clinical Features and Management of Congenital Hypothyroidism

Thyroid hormones play an important role in the neurocognitive development in the newborn period and infancy. Failure of the thyroid gland to secrete adequate amounts of thyroid hormones [T4 and triiodothyronine (T3)], regardless of its etiology, as well as any delay in the diagnosis of CH, will lead to worsening of the psychomotor development and somatic growth. The early clinical manifestations of hypothyroidism are very nonspecific and sometimes overlap with that of DS, leading to delayed diagnosis or misdiagnosis of CH. Hence, it is important to do repeat screening even after a negative newborn screening at birth, preferably earlier than the usually recommended screening at 6 months, for early detection of abnormalities in thyroid function.

The association between CH with thyroid dysfunction and gastrointestinal abnormalities such as duodenal atresia, anal atresia, and Hirschsprung disease remains unclear. The current management guidelines, including dosage for levothyroxine for CH, are the same as that for non-DS children.

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Acquired Hypothyroidism

Acquired hypothyroidism is also more common in DS than in the general population. Autoimmune thyroiditis (Hashimoto thyroiditis) is the most common cause of acquired hypothyroidism and is much more common than Graves' disease, another autoimmune disease affecting the thyroid in DS. The risk of developing autoimmune thyroid disorders increases with age.

Autoimmune Thyroiditis

Autoimmunity is more commonly seen with overt hypothyroidism than subclinical forms; hence, routine checking for autoimmunity is not recommended in DS children. Detection of anti-thyroperoxidase (TPO) antibodies is higher in DS compared to the general population. The detection of antithyroid antibodies, both anti-TPO and antithyroglobulin antibodies, is a good predictor for the severity of hypothyroidism. Older children with TSH levels >10 mU/mL should be evaluated for autoimmune etiology by checking TPO antibodies. Autoimmune thyroiditis in DS is characterized by less female preference, younger age at onset, lower antibody titer at diagnosis, and association with other autoimmune diseases. It requires treatment with thyroid hormone in addition to regular monitoring of thyroid function tests. Positive antithyroglobulin antibodies and anti-TPO antibodies were associated with higher odds of more severe hypothyroidism.

Hyperthyroidism

Hyperthyroidism or Graves' disease is rare in DS but more common than in the general population, with more than 100 cases reported in patients with DS globally. There are a few case reports from India with some cases initially diagnosed as SCH reverting to hyperthyroidism. Autoimmune thyroiditis may progress to Graves' disease more frequently in DS than in the general population. Most cases are detected in childhood and adolescence, and there is no gender predilection. The clinical features are similar to earlier presentation, less severe course characterized by heat intolerance, sweating, increased irritability, and weight loss, with diffuse goiter and rarely exophthalmos. Thyroid-stimulating immunoglobulin (TSI) levels are raised, and imaging confirms the diagnosis in most cases. A more frequent association with other autoimmune disorders is seen.

The course of Graves' disease is usually benign with good response to medical treatment with carbimazole or methimazole, and many of these cases will remit subsequently. Nonpharmacological modes of therapy, such as radioiodine or surgery, were rarely needed in a series from Italy, whereas iodine-131 was beneficial in those with shorter remissions or no remission after a mean period of 40 months on medical treatment in a series from Spain. Hypothyroidism is common following radioiodine therapy, and replacement therapy with levothyroxine is necessary.

GROWTH RETARDATION AND GROWTH HORMONE

Newborns with DS mostly have lower length, weight, and smaller head circumference at birth compared with control newborns. They have reduced linear growth potential with a blunted adolescent growth spurt. Thus, growth retardation is a cardinal clinical manifestation of DS beginning prenatally. It is most noticeable from the age of 6 months, and later during adolescence.

Disease-specific growth charts are helpful to monitor the growth of DS children and to detect further growth deviation due to associated comorbidities. The first DS-specific growth charts were prepared for the American population in 1998. The Centers for Disease Control and Prevention (CDC) of the USA currently recommends the use of revised growth charts. Many countries have developed their own disease-specific growth charts for DS. In a study from Sweden combining longitudinal and cross-sectional data, the mean birth length was 48 cm for both sexes and birth weight 3.0 and 2.9 kg, respectively, for boys and girls. Boys reached a final adult height of 161.5 cm and girls 147.5 cm at relatively young ages of 16 and 14 years, respectively. Head growth was impaired with an SDS of –0.5 at birth, decreasing to –2 at 4 years of age. A study from India observed significant growth retardation with length being more affected as age advanced, with body mass index (BMI) showing progressive increase with age.

Growth Hormone-Insulin-like Growth Factor 1 Axis

Short stature in DS has multiple etiologies. There is no overt deficiency of growth hormone (GH) or GH-releasing hormone (GHRH) in most studies, but it may occur secondary to pituitary or hypothalamic dysfunction.

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Selective insulin-like growth factor-1 (IGF1) deficiency is seen in children with DS >2 years with disruption of IGF1 signaling. A recent study summarized the pathogenesis of short stature to impaired GHRH–GH–IGF axis function, largely due to an abnormal quantitative and qualitative competence of the hypothalamic-pituitary axis and reduced bioactivity of endogenous GH. Other comorbidities such as congenital heart disease, thyroid dysfunction, celiac disease, obstructive sleep apnea, and feeding difficulties may aggravate growth retardation.

Growth Hormone Therapy in Down Syndrome

Early trials with recombinant GH had shown that GH therapy during infancy and childhood normalizes growth velocity and improves motor skill performance in DS. However, long-term studies did not show a positive increase in final height. A recent systematic review and meta-analysis evaluated the safety and efficacy of GH therapy in DS patients and assessed the ethical aspects of GH treatment in children with DS. Treatment with GH resulted in significantly higher growth velocity in the short term, suggesting that GH therapy should be considered in the long-term management of DS children. No significant adverse effects of GH treatment have been reported, but there is a caution about the increased risk for the development of leukemia. In addition, the improvement in psychomotor development with GH therapy is a factor in decision making for GH therapy. More long-term studies are necessary to make definite recommendations. At the time of writing, GH therapy is not approved by the US Food and Drug Administration or European Medicines Agency for the treatment of short stature in children with DS.

OBESITY AND OVERWEIGHT

Children with DS are more likely to be overweight or obese than the general population without DS. The combined prevalence of overweight and obesity varied between 23 and 70% in various studies, with the prevalence of obesity alone varying from 7 to 23%. Children with DS have a much more propensity for being overweight during the pubertal years. Typically, an infant with DS is underweight initially, but obesity sets in as age advances.

The factors leading to the development of obesity in DS are not very clear. It is attributed to decreased resting energy expenditure, decreased metabolic rate, decreased physical activity, unhealthy eating habits, and hypothyroidism. Obesity-related complications include obstructive sleep apnea, hyperinsulinemia, dyslipidemia, type 2 diabetes, and gait abnormalities. Body composition analysis with dual-energy X-ray absorptiometry (DXA) scans demonstrated that children with DS have decreased lean mass index and increased fat mass index.

Children with DS, especially those who are obese, may have an increased risk for cardiovascular disease and metabolic syndrome. A study from Chandigarh showed significantly higher leptin concentrations and higher indices of leptin resistance with low adiponectin levels in DS children compared to controls. Higher insulin resistance and lower adiponectin were also shown in another study, and their role as potential markers of metabolic syndrome needs further evaluation. The role of insulin resistance has not been thoroughly investigated in DS.

Overall, the prevalence of obesity leading to metabolic syndrome is higher in DS, and early preventive steps should be instituted in the young age group itself to prevent metabolic syndrome. Clinical evaluation and monitoring of BMI are advised in children with DS beginning at 2 years of age. Evaluation of obese children includes monitoring fasting blood glucose, fasting lipid profile, liver function tests, and glycosylated hemoglobin (HbA1C). These children and their families need appropriate counseling on lifestyle, diet, and physical activities.

GONADAL FUNCTION, PUBERTY, AND FERTILITY

Undescended Testes

Children with DS have a high incidence of cryptorchidism (6.5%), and ascending or acquired forms are common. Since there is a high chance for tumor development in DS children and testicular malignancy in cryptorchid testes, these children should be referred to pediatric surgeons early.

Hypogonadism

Primary gonadal deficiency is a well-known feature of DS; it is progressive from birth to adolescence and clearly manifests in adulthood. Children with DS have a higher level of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) compared to age-matched normal children, suggesting mild hypergonadotropic hypogonadism. This is progressive from birth to adolescence, often with delayed pubertal development. This is due to some

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amount of Sertoli and Leydig cell dysfunction in boys and ovarian dysfunction in girls. Boys with DS have lower total testosterone levels compared with controls due to Leydig cell dysfunction owing to the excess copy of genetic material of chromosome 21. Barring this, the onset of puberty is not much delayed in these children, and the majority of them will have normal pubertal progression. The disease-specific growth charts show that children with DS have a decreased pubertal growth spurt. Girls will need education regarding care during menstrual cycles, management of dysmenorrhea, and premenstrual symptoms.

In many cases, sex hormone levels are not very low, indicating their capacity to be fertile, and many married DS adults have children. In general, men with DS have lower fertility, but 70% of women with DS are fertile. The chances of miscarriage are higher. There is a 50% chance of having a child with DS and a higher chance of having other congenital anomalies. Hence, these children and their parents should be counseled properly about the issues in puberty, potential for fertility, and precautions to be adopted when these children are nearing adolescence.

DIABETES MELLITUS

Children with DS have a higher prevalence of diabetes mellitus than the general population. Both type 1 and type 2 diabetes have been reported in children with DS.

Type 1 Diabetes Mellitus

Type 1 diabetes is seen in around 2% of children with DS, with a 4-fold increase in the risk for development of type 1 diabetes compared with the general population of the same age. An earlier onset of type 1 diabetes in DS than general population is noted in some studies. Type 1 diabetes in DS is associated with increased subclinical islet cell autoimmunity with a lower frequency of the high-risk *HLA* genes. Type 1 diabetes in DS is also linked with other autoimmune diseases, mainly autoimmune thyroiditis and celiac disease. The expression of *AIRE* gene is also reduced in DS patients. These children usually have a better metabolic control despite lower insulin doses and lower rates of diabetes-related complications.

Type 2 Diabetes Mellitus

The reported prevalence of type 2 diabetes in children with DS ranges between 0 and 3.6%. The incidence increased with age, BMI, family history, and in girls, as shown in a report from Hyderabad. The association of type 2 diabetes in DS seems to be linked to sedentary lifestyle, obesity and metabolic diseases, and peripheral insulin resistance with declining β-cell function. Principles of management are the same as in the general population—lifestyle modification, weight loss, and oral antidiabetic drugs. The metabolic consequences of DS with type 2 diabetes require further validation.

DISORDERS OF BONE HEALTH

Defective bone strength with increased fragility and osteoporosis, leading to frequent fractures, is a common problem in DS. This is mainly due to faulty bone mineral accrual due to deficient intake of calcium and vitamin D. Lack of proper sun exposure, sedentary habits, poor muscle mass, malabsorption, and antiepileptic use are some of the etiological factors attributed to reduced bone mineral density (BMD) in these children. The bone mass of DS children may be exaggerated by the abnormalities in anthropometry and body composition. In addition, associated health issues such as developmental disorders, hypotonia of muscles, hypogonadism, growth retardation, and thyroid dysfunction may affect bone health.

There are very few studies that have evaluated the bone health and vitamin D status in DS. Some studies have evaluated bone density using dual-energy X-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT), or quantitative ultrasound (QUS). Children with DS have lower BMD compared to healthy controls, especially of the lumbar spine. There are no recommendations for periodic BMD scans in DS children as of now; however, it seems reasonable to do periodic scans in high-risk groups such as those with obesity, hypotonia, neuromuscular disability, or abnormal metabolic parameters.

There are only a few studies that have evaluated the vitamin D status by estimating 25-hydroxyvitamin D [25(OH)D] in children with DS, but the results are conflicting. A study from Italy demonstrated a high prevalence of vitamin D deficiency in all age groups of DS. The few studies about biochemical bone markers or the prevalence of fractures are not conclusive. More studies are needed, especially from the developing world. Ensuring proper vitamin D supplementation, calcium-containing diet (milk and milk products), regular weight-bearing exercises, and encouraging outdoor play for proper sun exposure will improve bone health in children with

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DS. There are no specific recommendations for vitamin D supplementation for DS. Current practice for vitamin D supplementation to prevent vitamin D deficiency is the same as for the general population.

AUTOIMMUNE DISORDERS

Children with DS are much more prone to autoimmune disorders such as type 1 diabetes mellitus, celiac disease, vitiligo, and alopecia areata, especially in the presence of autoimmune thyroiditis. The mechanism underlying the high frequency of autoimmune diseases in DS is not clearly established. The increased incidence of autoimmune disease in DS has been hypothesized to be attributable to:

- Altered immune function in DS, either humoral or cellular
- Mutations in the autoimmune regulator (*AIRE*) gene located in the 21q22.3 region, which regulates T-cell function and self-recognition, by coding for a transcription factor necessary for expression of tissue-restricted antigens (TRAs) in thymic epithelial cells
- Alterations in the regulation of pro- and anti-inflammatory cytokines
- The suppressive effect of interferon-alpha and its toxic effect on the thyroid gland
- Association with the DQA1 0301 allele linked to the increased association of autoimmune thyroid disease and celiac disease

There are no clear recommendations for routine screening for autoimmune disorders in children with DS.

Celiac Disease

Celiac disease is a common autoimmune disorder caused by gliadin and related proteins of wheat. It is very commonly seen in association with other autoimmune disorders and DS, the symptomatic form being more common than the asymptomatic. Studies have noted 6–10-fold increase in risk of developing CD for DS patients compared to the general population and affecting up to 7% of the DS children and GH deficiency. Nearly half of the children with CD do not have recognized symptoms, leading to a possibility of missed or delayed diagnoses. The European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommend screening all children with DS after age 3 years, and earlier if symptoms are apparent. The AAP, however, recommends only symptom-based screening from age 1. The significance of detecting CD early is its association with hypothyroidism, GH deficiency, type 1 diabetes, and other hormonal disorders, both in DS and the general population.

OTHER CHRONIC SYSTEMIC DISORDERS

Children with DS with CH are at increased risk of developing congenital anomalies, especially congenital heart diseases and gastrointestinal anomalies, compared to patients with DS and without CH. The inter-relationships of these disorders with endocrine comorbidities are being evaluated.

CONCLUSION

Current research has helped us to understand the pathophysiology and management of endocrine disorders associated with DS in children, which can impact their health and development. Thyroid dysfunction is common in individuals with DS, and early periodic screening is essential. Controversy remains regarding the treatment of SCH given unclear benefits. The use of disease-specific growth charts needs to be encouraged. There is no clear evidence to suggest routine GH therapy in DS children. Puberty develops normally in individuals with DS, and fertility is possible. Both obesity and overweight are common. Further research is needed in the field of BMD in DS. The pathophysiologic mechanism for the increase in autoimmune diseases is better understood now. There is a need to screen for both type 1 and type 2 diabetes. The efforts of the healthcare providers should be channeled to improve the life expectancy for individuals with DS and provide better opportunities to optimize medical management to reduce morbidity and maximize function.

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Down syndrome (trisomy 21) is a condition that every doctor interested in child health is definite to encounter. Despite its prevalence of approximately 1 in 700 live births, the management of this condition and the counseling of parents often remain neglected due to a lack of training or understanding of its multifaceted aspects. Early diagnosis and appropriate management can enable individuals with Down syndrome to lead near-normal, independent lives.

This book offers a comprehensive exploration of the challenges faced by individuals with Down syndrome and provides detailed current management guidelines. It also addresses the legal considerations and available support systems crucial for their well-being. With contributions from leading experts across India, the book comprises 28 chapters covering a wide range of topics, making it an invaluable resource.

The *IAP Textbook of Down Syndrome* emphasizes not only the medical management of the condition but also the importance of early intervention programs. By focusing on habilitation rather than rehabilitation, the book underscores proactive approaches to care and development. To the best of our knowledge, this is the first comprehensive reference textbook on Down syndrome authored from a developing country's perspective. It is designed to benefit doctors, general pediatricians, obstetricians, and medical students by providing an in-depth understanding of the condition and practical guidance for its management. Since the establishment of the Down Syndrome Trust (DoST) in 2000, the editor has been privileged to work with more than 2,000 children, helping them and their families navigate their unique journeys. This book is a reflection of that experience and the collective expertise of the contributors, aiming to inspire and guide others in providing holistic care for individuals with Down syndrome.



Shaji Thomas John MD DCH DTM&H PGDAP FIAMS FIAP (Hon) FNDP is Chief of Pediatrics and Neonatology, Baby Memorial Hospital, Kozhikode, Kerala, India. He is a renowned pediatrician with over two decades of experience in the management of children with Down syndrome. As the founder of the Down Syndrome Trust (DoST) in 2000, he has been instrumental in transforming the lives of over 2,000 children and their families through comprehensive care, early intervention programs, and advocacy. A leading voice in the field, he has contributed extensively to the understanding of Down syndrome in the Asia–Pacific region, emphasizing the importance of habilitation and holistic management.

His dedication, expertise, and compassionate approach have earned him recognition as a pioneer in advancing support for individuals with Down syndrome. He was instrumental in starting the department of pediatrics at Baby Memorial Hospital, Kozhikode, in 1987, which is now a tertiary care referral unit. He is a speaker for national and international conferences on Down syndrome and has various publications to his credit.

He has received various awards, including the Best Doctor Award of the state of Kerala and the Down Syndrome Federation of India Excellence Award.

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