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Original Article

Pattern and profile of different thyroid dysfunctions in Down Syndrome

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ABSTRACT

Thyroid disorders are one of the preventable causes of abnormal neurodevelopment in children. Congenital thyroid abnormalities are commonly observed in children with Down syndrome (DS), with previous studies indicating a higher incidence of conditions such as congenital hypothyroidism, subclinical hypothyroidism, and hyperthyroidism. Early detection and treatment are crucial, to prevent permanent neurodevelopmental impairments and other health issues. This retrospective study aimed to assess the prevalence and types of thyroid dysfunction in children with DS at the government Paediatrics hospital in Ras Al Khaimah, between January 2019 and July 2023. Ethical approval was granted by the University and the Ministry of Health Research Ethics Committee, and data were gathered from clinical records using a pre-designed format. Statistical analysis was performed using SPSS version 28, with descriptive statistics and two-sample t-tests to examine gender differences ($p < 0.05$) considered significant. The study included 31 genetically confirmed DS cases, with 61.3% male (19 cases) and 38.7% female (12 cases). The most prevalent thyroid dysfunction was congenital hypothyroidism (CH), found in 54.8% of the cases, followed by subclinical hypothyroidism in 38.7%, and hyperthyroidism in 6.4%. The most common etiology of CH was thyroid hypoplasia (71%), followed by thyroid ectopia (21%), athyreosis (5%), and partial agenesis (3%) in patients with DS. The results indicate that thyroid dysfunction is a significant concern in children with DS. The findings emphasize the need for routine screening for thyroid abnormalities as recommended by the American Academy of Pediatrics to ensure timely diagnosis and prevent complications associated with untreated thyroid abnormalities in this population.

Keywords: Down Syndrome, Thyroid abnormalities, Congenital hypothyroidism, Hyperthyroidism in Down syndrome, Autoimmune thyroid disease

Introduction

Down syndrome (DS) is one the most common chromosomal abnormalities among live-born infants and is associated with intellectual disability [1, 2]. The population estimates of DS show different prevalence worldwide with 8,031 annual DS live births in Europe, and between 1 in 1158 to 1 in 1,499 in Australia, New Zealand, and the United States of America [3-5]. The incidence of DS in the United Arab Emirates is 1 in 374 live births (267 in 10,000 live births, making it the most common genetic abnormality in live births [6]. The DS phenotype and intellectual disabilities vary among patients, ranging from mild to severe. The social functions are also affected but are mostly higher than cognitive functions [2]. As has long been recognized, DS occurs due to an extra set of Chromosome 21, resulting in trisomy 21. The clinical features of the syndrome have been attributed to the genes on chromosome 21, as well as epigenetic factors [7]. The trisomy can occur due to non-disjunction, or translocations from others to chromosome 21. There can be also partial trisomies and mosaicism. While the clinical features do not differ between

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cases with non-disjunction, or translocations, it is milder with fewer features in partial trisomies and mosaicism [2]. The most accurate initial diagnostic assessment is a thorough physical examination and diagnosis is suggested by body habitus and physiognomic features, accompanied by muscular hypotonia. Confirmation of diagnosis is done by genetic testing. Karyotype reliably diagnoses translocation or nondisjunction as the causative factor.

DS is linked to an increased incidence of endocrine abnormalities, particularly thyroid gland disorders. It is estimated to occur in 4- 8% of children with DS. Abnormalities include subclinical hypothyroidism, congenital hypothyroidism, acquired hypothyroidism (autoimmune – non-autoimmune), and hyperthyroidism [8]. Untreated thyroid disorders can cause significant preventable secondary neurodevelopmental impairment and other health issues [9]. Thyroid hormones are vital for the development of the central nervous system, particularly during infancy. Failure of the thyroid gland to produce an adequate amount of thyroid hormones and delay in diagnosis of hypothyroidism in DS children will result in worsening of psychomotor development, somatic growth, and mental retardation [9, 10]. In this regard, the American Academy of Pediatrics recommends thyroid function screening in children with DS at birth, 6 months, 12 months, and yearly. Therefore, screening for thyroid abnormalities at the recommended interval is crucial [11]. Like other genetic diseases, DS is also associated with other associated abnormalities [12, 13]. In DS it includes developmental disabilities as well as medical diseases such as congenital heart disease, pulmonary abnormalities, sleep-related breathing disorders, and endocrine dysfunction. Children with DS have a higher likelihood of developing endocrine disorders such as thyroid dysfunction, diabetes mellitus, short stature, vitamin D deficiency, and obesity than the general population [11]. Both DS and thyroid abnormalities can adversely affect neurodevelopment, cognitive functions, and intellectual abilities in individuals. It has also been reported that there are differences in the incidence and presentation of DS according to ethnic background and geographic region [2]. Hence, this study investigates the pattern and profile of thyroid dysfunction in children with DS at a center in the United Arab Emirates.

Materials and Methods

This study is a retrospective study conducted at a single center at the Department of Pediatrics and Neonatology, at Saqr Hospital, Ras Al Khaimah, UAE. Ethical clearance was obtained from Ras Al Khaimah Medical and Health Sciences University Research Ethics Committee and the Ministry of Health Research Ethics Committee. The study included DS cases with thyroid dysfunction, from January 2019 to July 2023. The study population consists of genetically confirmed DS cases attending the pediatric department during the specified time frame. Inclusion criteria encompassed all genetically confirmed DS cases, while exclusion criteria applied to suspected cases of Trisomy 21 without karyotype confirmation and other trisomies. Consecutive sampling was employed, including all DS patients visiting the pediatrics department during the period. Parents were also contacted for follow-up data over the four years after ethical approval and provided with information about the study. Their consent was obtained, and up-to-date data regarding the current state was gathered. Data were collected using a pre-designed format, including relevant clinical and investigative information from hospital records. Data analysis was performed using SPSS version 28.0.1, with descriptive statistics used to summarize the data. A two-sample t-test was employed to compare the responses of males and females, with a significance threshold of $p < 0.05$.

Results and Discussion

Among the 31 Down Syndrome (DS) cases surveyed, 61.3% were male (19 cases) and 38.7% were female (12 cases). All the cases identified were genetically confirmed and were trisomy 21. No cases were identified with partial trisomies or mosaicism. The most prevalent thyroid dysfunction observed in these patients was congenital hypothyroidism (CH), which was present in 54.8% of the cases. This was followed by subclinical hypothyroidism (SH) in 38.7% of cases, while 6.4% of the patients had hyperthyroidism **(Figure 1)**.

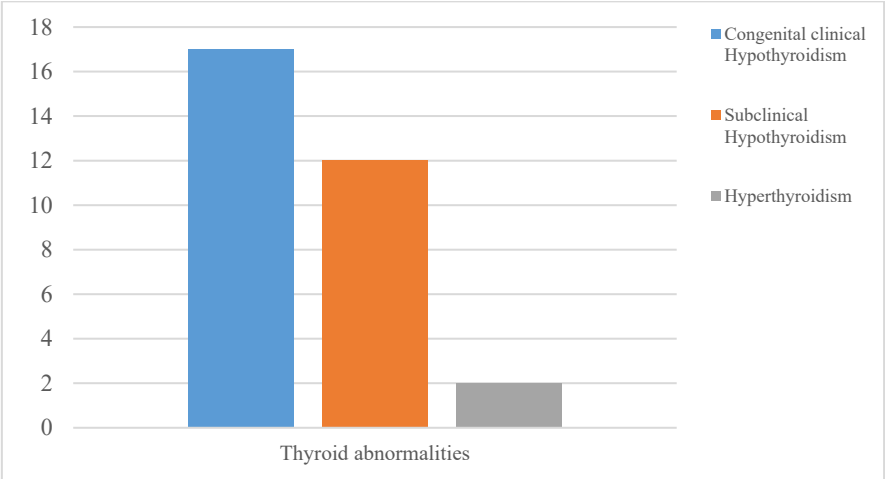


Figure 1. Prevalence of different thyroid abnormalities in Down Syndrome

CH is a thyroid dysfunction diagnosed at birth, characterized by elevated plasma Thyroid Stimulating Hormone (TSH) levels (>10 mIU/l) and low plasma Thyroxine (T4) levels [14]. It is often detected through neonatal screening programs, and the prevalence of CH in individuals with DS is estimated to be 28-35 times higher than in the general population [1]. Our study identified that thyroid hypoplasia was the most common etiology of CH in DS, accounting for 71% of cases, followed by thyroid ectopia (21%), athyreosis (5%), and partial agenesis (3%). This study also investigated the clinical features, prevalence, and outcomes of CH in DS, highlighting key findings that contribute to our understanding of thyroid dysfunction in this population.

Prevalence and gender differences in CH in Down Syndrome

Our study did not find the typical female preponderance observed in the general population with CH. This aligns with previous reports indicating that gender distribution patterns for CH may be altered in certain genetic syndromes, including DS. While females generally have a higher incidence of CH in the general population, the altered pattern in DS suggests that genetic factors and the underlying pathophysiology in DS might influence the gender distribution of thyroid dysfunction [15]. This finding warrants further exploration in larger studies to understand the mechanisms that might contribute to this unusual distribution in DS.

Types of congenital hypothyroidism

Our study identified that thyroid hypoplasia was the most common etiology of CH in DS, accounting for 71% (n=12) of cases **(Figure 2)**. These findings are consistent with the broader literature on CH, where thyroid hypoplasia is the most frequent cause of the condition. The relatively high incidence of thyroid ectopia and partial agenesis may be particularly noteworthy in DS, as it could reflect the unique developmental aspects of the thyroid gland in individuals with chromosomal abnormalities [16, 17]. Understanding the specific pathophysiological mechanisms involved in thyroid development in DS could provide insight into why these anomalies are more frequent in this population.

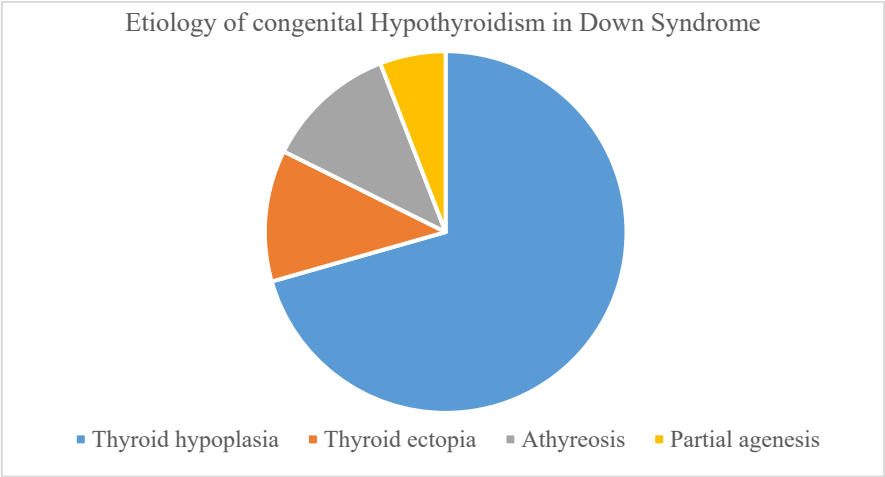
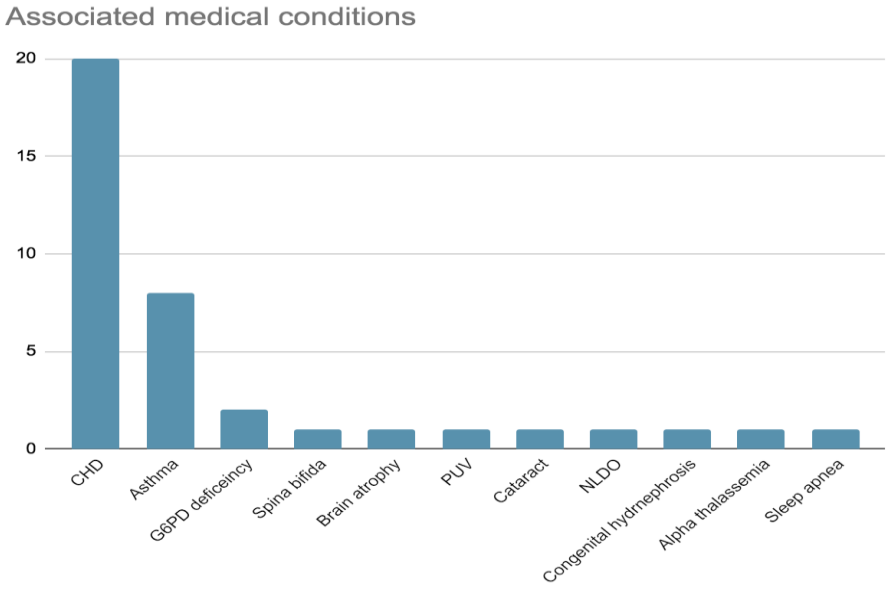


Figure 2. Etiology of Congenital Hypothyroidism in Down Syndrome

Association with other anomalies

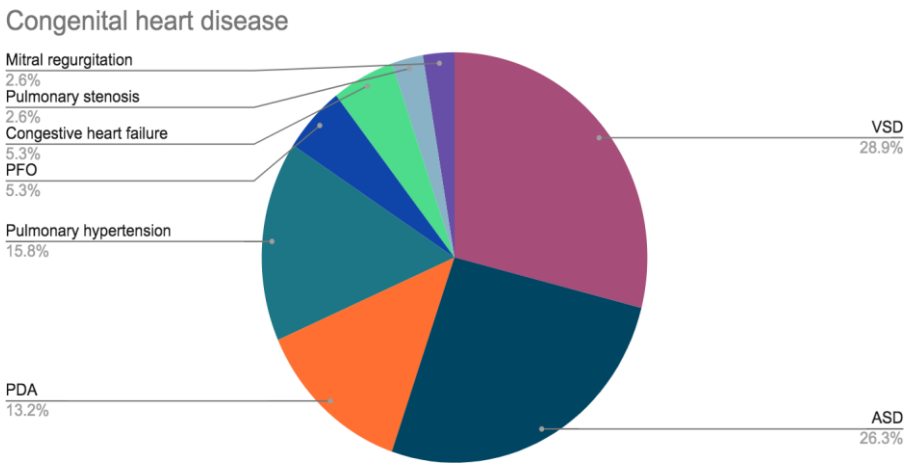
In addition to thyroid dysfunction, we observed a higher association of CH with other congenital anomalies in DS, particularly congenital cardiac disease, respiratory distress syndrome, and gastrointestinal anomalies. The most common association was congenital heart disease followed by asthma **(Figure 3)**. The range of detected heart conditions included ventricular septal defect (most common 28.9%), Atrial septal defect (26.3%) to pulmonary stenosis (2.6%) **(Figure 4)**. These comorbidities have been well-documented in DS and may reflect the multi-organ involvement characteristic of this genetic condition [18-20]. Pulmonary artery hypertension (PAH) was seen in 15% of patients in our study. Children with DS are usually present with associated obstructive sleep apnea, gastroesophageal reflux, and obesity along with PAH. Hence, surveillance for PAH throughout childhood is indicated, for early detection and intervention to prevent complications [21, 22]. Sleep apnea was found in one patient with PAH, and DS in this study. The child is undergoing regular follow-up. Another systematic review reported osteopenia/ osteoporosis, hearing impairment, cervical spine, and sleep apnea as associated abnormalities in DS, in addition to thyroid abnormalities and heart disease [23]. Congenital heart defects (72.23%), and malocclusions (58.62%) were also reported in a significant number of children with DS, in another study involving 763 children [20]. However, we did not detect any hearing impairment, or dental problems among participants in this study. A recent study reported various ophthalmologic manifestations of DS including strabismus, amblyopia, refractive error, eyelid abnormalities, nasolacrimal duct obstruction, nystagmus, keratoconus, cataracts, retinal abnormalities, optic nerve abnormalities, and glaucoma [24]. The prevalence was significantly higher in DS compared to the general population. We did not find abnormalities other than nasolacrimal duct obstruction. A co-existence of CH and gastrointestinal anomalies is observed in DS in our study. Studies reported that Down syndrome babies with gastrointestinal anomalies at birth were

8.6 times more likely to have CH [25]. Other endocrine abnormalities seen in DS are diabetes Mellitus and gonadal dysfunction [26]. However, these were not detected in our study. The association of asthma, posterior urethral valve, hematological disorders, and hydronephrosis are also rarely reported in the literature. The presence of multiple congenital anomalies in DS children with CH raises the importance of early screening and comprehensive care to manage the complex clinical picture in these patients.



[CHD= Congenital heart Diseases; G6PD= Glucose 6 Phosphate Dehydrogenase; PUV= Posterior Urethral Valve; NLDO= Nasolacrimal duct obstruction]

Figure 3. Associated medical conditions with thyroid abnormalities in children with Down syndrome



[VSD= Ventricular septal defect; Atrial septal defect=ASD; PFO= Patent Foramen Ovale]

Figure 4. Spectrum of associated congenital heart diseases with thyroid abnormalities in babies with Down syndrome

Subclinical hypothyroidism in DS

We also examined SH in our study, which is characterized by isolated elevation of TSH with normal thyroid hormone levels. SH is often referred to as "mild hypothyroidism" or "compensated hypothyroidism" and may remain asymptomatic for extended periods. In our study, the majority of patients with SH had a TSH level between 5-10 µIU/mL, with a mean TSH level of 7.9 µIU/mL. This is consistent with the definition of SH as a mild form of thyroid dysfunction that does not typically present with the overt clinical symptoms of hypothyroidism, such as hypotonia or weight gain [17, 27]. Interestingly, positive thyroid antibodies (thyroid peroxidase antibodies and autoantibodies to thyroglobulin) were found in 16.1% of all SH cases. The presence of thyroid antibodies was more likely in cases with higher TSH levels (>10 µIU/mL), suggesting an autoimmune component in the pathogenesis of SH. This is consistent with previous studies that report an increased prevalence of autoimmune thyroid disease in individuals with DS, a population already predisposed to autoimmune disorders [15]. However, the prevalence was higher in our study compared to other research which reported SH as the most common

thyroid abnormality (24%) in patients with DS involving 508 patients [14, 28-30]. The neonatal screening at birth using T4 levels may miss a significant proportion of hypothyroidism, and it is recommended that screening need to be repeated in individuals with DS [31].

Natural history of subclinical hypothyroidism

Another important finding from our study is the spontaneous resolution of SH in two-thirds (n=6) of the cases, with only one-third (n=3) progressing to overt hypothyroidism. These findings are consistent with previous literature indicating that SH in neonates and infants are not always precursors of hypothyroidism, and may resolve over time, particularly in the absence of autoimmune antibodies [32, 33]. The absence of symptoms in the majority of SH cases suggests that regular monitoring, rather than immediate intervention, may be an appropriate management strategy in certain cases. However, we observed that two of the SH cases with thyroid antibody positivity at TSH levels much below the recommended level (>10 μIU/mL) did not show remission, suggesting that their presence may be a risk factor for progression to overt hypothyroidism. The pattern of TSH and T4 elevations in DS was explored by another study reporting a much higher trend in DS compared to the general population [34-37]. *The authors suggested the mechanism being resetting of the hypothalamic-pituitary-thyroid axis.* This finding underscores the importance of long-term monitoring and early intervention in SH cases with positive thyroid antibodies to prevent progression to more severe forms of thyroid dysfunction. The autoantibodies in our study were found in patients.

Progression of SH to overt hypothyroidism

The incidence of progression from SH to overt hypothyroidism is reported to be less than 33%, and our findings align with this estimate [38-40]. However, the presence of thyroid antibodies appears to increase the risk of progression [39]. *There is considerable debate on whether treatment needs to be initiated at TSH values less than 10* μIU/mL in SH in vulnerable groups such as DS. A randomized control trial by Van Trostenburg *et al*. involving 224 patients with DS reported mild improvements in motor development and height in treated infants at 2 years of age [41] but not at 5 or 10 years [42, 43] Hence, it is suggested that SH may not need treatment below the level of *10* μIU/mL [37, 44]. This emphasizes the need for careful follow-up and possibly early thyroid hormone replacement therapy in individuals with SH and autoimmune thyroiditis, especially those with higher TSH levels or antibody positivity.

Hyperthyroidism in Down Syndrome: autoimmune diseases

In our study, autoimmune Graves' disease was identified as the main cause of hyperthyroidism in individuals with DS (n=2), both of whom were symptomatic very early in life. Although hypothyroidism is common in DS, hyperthyroidism was reported only in a few previous studies [23, 45]. Autoimmune thyroid diseases including Graves' disease and Hashimoto's thyroiditis, are more prevalent in individuals with DS compared to the general population [15, 46]. The autoimmune nature of hyperthyroidism in DS may be explained by an altered immune system, which predisposes individuals with DS to autoimmune disorders. It is also reported that patients with Hashimoto's thyroiditis (another autoimmune disease) and DS, progress to Grave's disease more often than the general population, and hence treatment with methimazole is recommended [28, 47, 48]. Both patients with hyperthyroidism responded well to initial methimazole treatment, with persistent remission after an initial dose of 0.38 ± 0.12 mg/kg/day. The guidelines in countries like the United Kingdom and Ireland also suggest testing for autoantibodies during each thyroid screening [49]. This suggests that early intervention with antithyroid medications can be effective in managing hyperthyroidism in this population, and close monitoring is essential for ensuring long-term control.

The limitations of this study are that it included patients from only one center with limited numbers available. The strengths included the cases being genetically confirmed, extensively evaluated, and investigated.

Conclusion

Recent advances have enhanced our understanding of the mechanisms behind thyroid dysfunction in DS, revealing distinctive patterns in the presentation of autoimmune thyroid disease. The progression of thyroid autoimmunity in DS is common and requires careful, ongoing follow-up. For subclinical hypothyroidism, a "watchful waiting" approach is becoming more prevalent, with more frequent monitoring recommended. While methimazole remains effective for managing hyperthyroidism, there is increasing evidence supporting the use of radioactive iodine for Graves' disease. However, there is still no universally accepted consensus on the optimal screening frequency after the first year of life or the TSH threshold for initiating treatment. Further research and standardized guidelines are needed to refine management strategies for thyroid dysfunction in DS.

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Conflict of interest: None

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Ethics statement: "The study was conducted following the Declaration of Helsinki, and approved by the Ethics Committee of RAK Medical and Health Sciences University, and Ministry of Health (MOHAP/REC/2023/40-2023-UG-M dated 12/12/2023).

Consent form for participation was distributed to all eligible participants and signed.

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