

Down Sendromlu Hastalarda Tiroid Disfonksiyonu; Klinik ve Kromozom Korelasyonu

Thyroid Dysfunction in Down syndrome Patients; Clinical and Chromosomal Correlation

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ÖZ

Amaç: Otoimmün hastalıkların Down sendromlu kişilerde, özellikle hipotiroidizmde meydana geldiği bilinmektedir. Bu çalışmanın temel amacı, Down sendromlu hastalarda anormal tiroid fonksiyonunun sıklığını tahmin etmek ve Irak, Duhok eyaletindeki yaş, kraniyofasiyal özellikler ve kromozomal anormalliklerin türü ile ilişkilerini değerlendirmektir.

Materyal ve Metot: Çalışmaya Down sendromlu 58 hasta dahil edilmiş; hepsi ana kraniyofasiyal özelliklerin varlığı açısından incelenmiştir. Tiroid fonksiyon testi ve kromozomal analiz için karyotipleme yapmak için olgulardan kan örnekleri alındı.

Bulgular: Down sendromlu 58 hastanın 25'inde (% 43.11) subklinik hipotiroidi vardı. Yaş grubu ile subklinik hipotiroidi yüzdesi arasında istatistiksel anlamlılık yoktu. En sık görülen kraniyofasiyal özellik, nispeten yüksek bir subklinik hipotiroidizm yüzdesine sahip epikantal kıvrımlar olmasına rağmen bu sonuç istatistiksel olarak anlamsızdı. Trizomi 56 (% 96.56) hastada en sık görülen kromozomal anormallik iken olgulardan sadece 2 (% 3.45) mozaikti. Translokasyon tespit edilmedi. Tüm hipotiroidizm vakaları Trizomi 21'in sayısal kromozomal anomalisidir.

Sonuç: Subklinik hipotiroidi, Down sendromlu hastalarda görülen ve tüm yaş gruplarında anlamlı farklılık göstermeyen en yaygın tiroid fonksiyon bozukluğuydu.

Anahtar Kelimeler: Down sendromu, kromozomal anormallikler, tiroid fonksiyonu

ABSTRACT

Objective: Autoimmune diseases are known to occur in people with Down syndrome, especially the hypothyroidism. The main objectives of the present study were to estimate the frequency of abnormal thyroid function in Down syndrome patients and to assess their relation to the age, craniofacial features and the type of chromosomal abnormalities in Duhok province, Iraq.

Materials and Methods: The study included fifty eight patients with Down syndrome; all of them were examined for the presence of the main craniofacial features. Blood samples were collected from them to perform the thyroid function test and the karyotyping for chromosomal analysis.

Results: Out of 58 patients with Down syndrome, 25 (43.11%) had subclinical hypothyroidism. There was no statistical significance between age group and percentage of subclinical hypothyroidism. The most frequent craniofacial feature was the epicanthal folds with a relatively high percentage of subclinical hypothyroidism, but this result was statistically insignificant. Trisomy was the commonest chromosomal abnormality seen in 56(96.56%) patients and only 2(3.45%) were mosaic. No translocation was detected. All the cases of hypothyroidism were numerical chromosomal abnormality of Trisomy 21.

Conclusions: The subclinical hypothyroidism was the commonest thyroid dysfunction seen in Down syndrome patients with no significant differences in all age groups.

Keywords: Chromosomal abnormalities, Down syndrome, thyroid function

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INTRODUCTION

Down syndrome (DS) is one of the most common chromosomal aneuploidy and the best known of all malformation syndromes, with an estimated prevalence of 1 per 650-1000 births worldwide. The incidence of DS in Duhok province of Iraq is 1/960, which is within the world average.^{1,2}

Down syndrome is associated with mental retardation, metabolic and endocrine disorders, several congenital anomalies, including cardiovascular and gastrointestinal systems. The most frequent endocrine disorders associated with DS are thyroid related disorders.³ Different autoimmune conditions may affect DS patients, especially the hypothyroidism that might appear at birth or later in life. It has been found that congenital hypothyroidism may affect DS patients 28 times more than the general population.⁴ In general, the signs and symptoms of hypothyroidism include dry and rough skin, tiredness, intolerance, constipation, drowsiness, apathy, motor clumsiness, weight gain, change in voice tone, and macroglossia. Most of these signs are frequent in individuals with DS.⁵

Alterations of thyroid function frequently occur throughout the life of DS patients. If these dysfunction left untreated may affect the development and quality of life. Therefore, accurate diagnosis is an essential step to treat this dysfunction. It is reported that 1% of people with DS might develop hypothyroidism at birth, but this percentage increase with age, therefore, it is recommended to assess the thyroid stimulating hormone (TSH) annually.⁶

The early detection of DS is an essential step to maximize cognitive abilities in this already impaired population. The health supervision guidelines for children with DS suggested reviewing results of the newborn thyroid function screen, then repeating thyroid function tests annually.⁷

The elevated TSH, normal triiodothyronine (T₃) and thyroxine (T₄) levels is defined as subclinical hypothyroidism. Previous studies reported that the subclinical hypothyroidism is the most common thyroid condition in this syndrome, and since the hypothyroidism or thyroid dysfunction can be congenital or acquired in patients with DS, therefore, these patients should be followed up periodically test for thyroid functions since birth.^{8,9}

The present study aims to determine the frequency of thyroid dysfunction and hypothyroidism in patients with DS and their correlation with the patient's age, and other clinical features, including the

craniofacial features of DS, that might differ according to the severity of the disease, and with the type of chromosomal abnormalities in the affected patients in Duhok province, Iraq.

MATERIALS AND METHODS

Sample collection and ethics Statement: This is a cross-sectional descriptive study, which included 58 DS patients from Duhok province. The study was conducted from April 2019 to September 2019 and the ethical approval (Date: 06.02.2019 and Decision no: 79) was obtained from the college of medicine research ethics committee, and permissions from all children parents have been taken.

Patients were examined and filled a list of the craniofacial feature, which included: Up-slanting palpebral fissures, epicanthic folds, open small mouth, protruding tongue, depressed nasal bridge, high arched palate, furrowed tongue, flat facial features, low set, small ears, flat occiput (Brachycephaly), Hypertelorism (increase in the inter-orbital distance), open fontanel, short neck, excessive skin folds on neck and microcephaly.

Blood samples were collected from patients for chromosomal study and the assessment of the thyroid function by estimating the TSH, free T₄ and T₃ levels. The cytogenetic analyses and karyotyping were performed at the college of medicine, university of Duhok.

The thyroid function test was carried out by obtaining 500 µl of serum sample from patients, then measure the levels of TSH, T₃ and T₄ by MAGLUMI 1000 Chemiluminescence immunoassay (CLIA). The following standard normal ranges were depended: TSH: 0.3-4.5 uIU/ml, T₃: 0.69-2.15 ng/ml and T₄ 52-127 ng/ml. The Types of thyroid dysfunction were categorized into hypothyroidism, subclinical hypothyroid and hyperthyroid status according to the criteria shown in [Table 1](#).

Karyotype analysis: The chromosomal analysis was carried out by adding 0.5 ml of peripheral blood to a culture tube containing 10 ml of culture solution (RPMI 1640 with L-glutamine, Phytohemagglutinin, Fetal bovine serum, Penicillin-Streptomycin) and incubated for 72 hours at 37°C, and then 200µl of Colcemid were added. After 1 hour, mixture were treated with hypotonic solution (KCL 0.25 in 50 ml distilled water) and fixation solution (Methanol: Glacial acetic acid 3:1), and then slides prepared and stained with Geimsa stain to detect chromosomal abnormalities.

Statistical analysis: Data analysis was performed by using IBM SPSS Statistics software version 22. Descriptive data were presented for continuous variables as mean \pm SD, while qualitative data description done by calculating numbers and percentages. T-test was used to compare between two means and Chi-square (χ^2) tests used to compare between proportions, The P value ≤ 0.05 considered statistically significant.

RESULTS

Demographic study: The present study performed on patients who were clinically diagnosed as DS. The age of the participants patients ranged from 6 to 18 years with a median age of 11 years (mean 11.32 ± 7 years). Out of the 58 cases, 31 (53.44%) were males and 27 (46.56%) were females with male to female ratio of 1.14:1.

Out of the 58 patients, 33 (56.89%) had normal thyroid function values, while 25 (43.11%) patients had subclinical hypothyroidism. The distribution of these 25 patients by the age groups is seen in [Figure 1](#). Although a large number of the studied group (32 cases) was within the age group of 10-15 years, the subclinical hypothyroidism was distributed on all age group as follow: 28%, 60% and 12% for the patients less than 10 years, between 10-15 years and more than 15 years respectively. No statistical difference was seen between the distribution of these three age groups and the presence of subclinical hypothyroidism.

The most frequent craniofacial feature in this study was the epicanthal folds which present in 43 cases (74.1%) in all age groups. A relatively high percentage of subclinical hypothyroidism was seen in these patients also but this result was statistically insignificant. The other three common features were; up-slanting palpebral fissures, protruding tongue and depressed nasal bridge. The correlation of all craniofacial features with the age groups and the subclinical hypothyroidism in the patients with DS is presented in [Table 2](#).

Cytogenetic and chromosomal analysis: The cytogenetic analysis for all patients with DS showed that the numerical abnormality of Trisomy 21 was the most common type of abnormality which detected in 56 cases (96.5%), while only 2 cases (3.5%) showed mosaicism and no chromosomal translocation was seen. All the cases of subclinical hypothyroidism (25 cases) found to be of numerical chromosomal abnormality of Trisomy 21, while the two cases of mosaic chromosomal abnormality where of normal thyroid

function test.

The types and percentages of chromosomal abnormalities detected in all cases are shown in [Table 3](#).

DISCUSSION AND CONCLUSION

The incidence of Down syndrome in Duhok province of Iraq is approximately 1/960 live births, which is within most international ranges, especially with countries in the region like Turkey (1/1000 live births) and Iran (1/900 live births).^{1,10,11} The present study showed a relatively high incidence of subclinical hypothyroidism in patient with DS in Duhok province (43.11%). In fact, the diagnosis and treatment of hypothyroidism in patients with DS are mostly depending on the clinical symptoms and the results of blood tests of TSH which is produced by the pituitary gland at the base of the brain. The high level of TSH and low level of thyroxin consider as a significant indicator to hypothyroidism condition. Increase the production of TSH stimulating thyroid gland to produce more thyroid hormone.¹² Therefore the American Academy of Pediatrics recommended thyroid hormone testing for DS infants at birth and at 6 and 12 months of age. Even adult patients with DS must check their TSH level regularly, this will help health care professional in managing hypothyroidism since it helps them to determine the right dosage of medication, both initially and long term dose.¹³

Thyroid hormones have a vital role for the development of the central nervous system during childhood, especially in the migration and differentiation of neuron and activation of the sympathetic nervous system. When hypothyroidism left untreated, may aggravate several complications correlated with DS during infancy and childhood, such as psychomotor development, somatic growth and mental retardation.¹⁴

The association between DS and thyroid dysfunction is well recognized. Previous works were investigated the association between DS and thyroid dysfunction, for instance, ; some authors reported that neonates suffer from hypothyroidism 28-times more than the normal newborns.¹⁵ *Gibson et al.*, (2005) conducted study focus on DS children on different ages and at two different time period. This study demonstrated that these abnormalities were decreased with age.¹⁶ However Predieri and his co-workers found that the normal thyroid function values in patients with DS were significantly decreasing over a period of 10-year follow-up.¹⁷

Unlike these two researches the current study found

no significant differences among the patients; below 10 years, between 10-15 and those over 15 years. It is difficult to compare these results with normal population who suffer from thyroid dysfunction since the data available of this disease in newborn are uncertain. Therefore, it is important to have registration of all patients with DS so that timely screening for hypothyroidism can be performed.¹⁵

On the other hand, Wassner and Brown found that there is increasing in incidence of hypothyroidism in newborns in general, and they stated that [Primarily due to increased stringency of screening strategies, with smaller contributions from changing demographics and improved survival of increasingly premature infants].¹⁸

The commonest four craniofacial features in this study were the epicanthal folds, the up-slanting palpebral fissures, the protruding tongue and the depressed nasal bridge. However the karyotyping is important to confirm the diagnosis.

The current study showed that most DS patients had numerical abnormality of Trisomy 21 and all the cases of subclinical hypothyroidism were of this category. Unfortunately, the low number of mosaicism patients made the statistical analysis between patients with normal thyroid function values and those with the subclinical hypothyroidism insignificant. Further studies with larger number of DS patients need to be performed to get representative results.

In conclusion; the present study concluded that Thyroid dysfunction, which represented by the subclinical hypothyroidism, is common in children with DS and distributes in all age groups with no significant differences. Consequently, this study recommended annual screening for SD patients as a prophylactic step.

Ethics: This study started after the approval of the Duhok medical scientific and ethical committee (Date: 06.02.2019 and decision no: 79)

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept-DS; Supervision-MY; Materials-RM; Data Collection and/or Processing-DF; Analysis and/ or Interpretation – DS, MY; Writing-DS.

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Table 1. Types of thyroid dysfunction.

Thyroid dysfunction	Description
Over hypothyroidism	Elevated TSH along with reduction in T ₃ and T ₄ indicates
Subclinical hypothyroidism	The serum level of TSH from the front of the pituitary gland is a little bit above normal while the thyroid hormones produced by the thyroid gland are still within the laboratory's normal range
Hyperthyroidism	Elevated T ₃ and T ₄ indicate

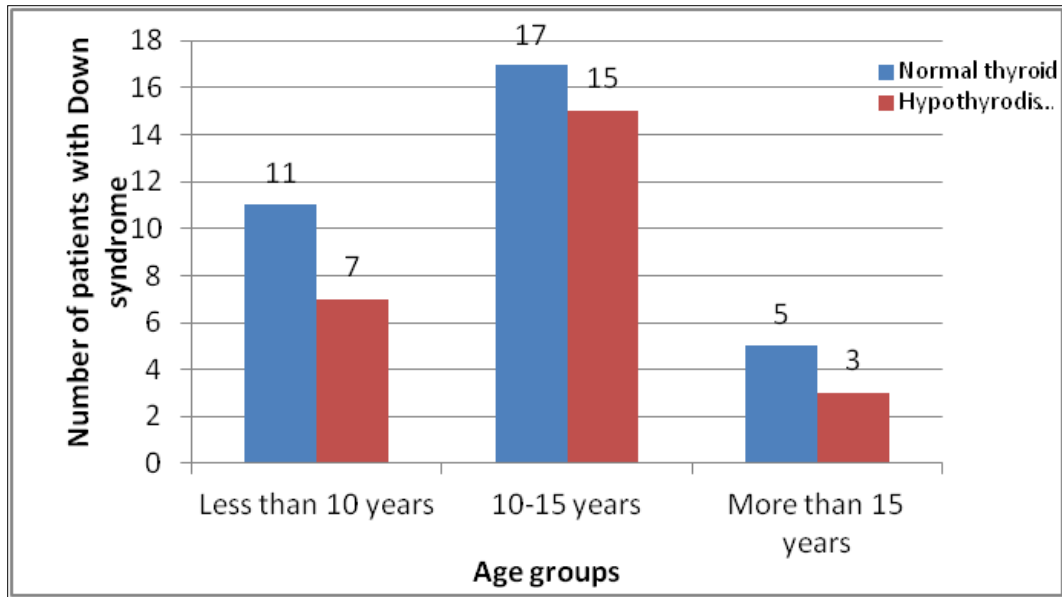


Figure 1 The correlation between the age groups and the subclinical hypothyroidism in patient with Down syndrome.

Table 2. The correlation between the craniofacial features and the subclinical hypothyroidism in patient with Down syndrome.

Craniofacial features	Age groups				Thyroid function status
	Less than 10 years	10-15 year	More than 15 years	Total	Subclinical hypothyroidism
	(18 cases)	(32 cases)	(8 cases)		
Epicanthal folds	13	23	7	43 (74.1%)	17 (29.3%)
Up-slanting Palpebral fissures	11	22	4	37 (63.8 %)	15 (25.9%)
Protruding tongue	11	17	7	35 (60.3%)	17 (29.3%)
Depressed nasal bridge	9	20	6	35 (60.3%)	16 (27.6%)
Low set, small ears	9	18	4	31 (53.5%)	16 (27.6%)
Flat facial features	12	15	4	31 (53.5%)	10 (17.2%)
Short neck	10	15	3	28 (48.9%)	12 (20.7%)
Brachycephaly	10	13	3	26 (44.8%)	13 (22.4%)
Hypertelorism	8	13	4	25 (43.1%)	11 (19.0%)
Microcephaly	10	12	2	24 (41.4%)	12 (20.7%)
Furrowed tongue	8	14	2	24 (41.9%)	10 (17.2%)
Open fontanel	6	6	3	15 (25.9%)	7 (12.1%)
High arched palate	2	12	1	15 (25.9%)	8 (13.8%)
Excessive skin folds on neck	7	7	1	15 (25.9%)	7 (12.1%)

Table 3. The frequency and percentages of chromosomal abnormalities.

Chromosomal abnormality	Karyotype	Frequency	%
Trisomy 21	[47,XY,+21]	31	(53.44%)
	[47,XX,+21]	25	(43.11%)
Mosaic	[46,XX/47,XX,+21]	2	(3.45%)
Translocation	Not found	0	(0.0%)