The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 2486-2490

Assessment of Thyroid Dysfunction in Children with Trisomy 21 and Cardiac Abnormalities

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ABSTRACT
Background: Developmental difficulties, muscle hypotonia, small stature, unique facial traits, and congenital abnormalities, notably cardiac, are all phenotypic aspects of Down syndrome. **Aim and objectives:** to assess thyroid function abnormalities in children with Down syndrome and congenital heart disease. **Subjects and methods**: The study was conducted at Cardiology Unit of Pediatric and Neonatology Department at Zagazig University Hospitals as a cross-sectional study on 50 subjects, Patients were evaluated for congenital heart disease using plain chest X-ray, electrocardiography, two-dimensional echocardiography and Doppler studies. Thyroid function parameters were also performed including plasma TSH, FT3 and FT4. **Results:** Highly significant differences were found between the studied groups as regard TSH, FT4 and FT3 levels, but no statistically significant differences between them as regard age or gender. In addition, there was no significant relation between genetic types of Down syndrome and thyroid function. **Conclusion:** Thyroid dysfunctions, most commonly subclinical hypothyroidism, are frequent in children with Down syndrome, with no relation of length, weight, maternal age or gender to the thyroid function.
Keywords: Cardiac Abnormalities, Thyroid Dysfunction, Trisomy 21.

INTRODUCTION
Having an extra copy of the chromosome 21 genetic material is a chromosomal anomaly known as Down syndrome (DS). DS is the most prevalent chromosomal abnormality in humans and the most common cause of severe learning difficulties, with an incidence of 1:800 live births [(1)].

Trisomy 21 is more likely to occur in mothers who are older than 35 years old. There are more than 80 distinct features that define this illness. The most common phenotypic manifestations are developmental difficulties, muscle hypotonia, small stature, certain facial traits, and congenital abnormalities, particularly heart problems. To begin with, the DS phenol form was created as a result of an imbalance in the chromosomes. The lack of phenotypic heterogeneity in other autosomal trisomies cast doubt on this notion. In patients with incomplete chromosome 21 trisomy, genotype and phenol type correlations reveal that the limited area in 21q 22.2 is associated with the key clinical aspects of DS. This is in accordance with the gene-dose-effect theory [(2)]. One of the most common causes of infant mortality and morbidity in people with Down syndrome (DS) is congenital heart disease (CHD) syndrome, which affects 40 to 63.5 percent of patients [(2)].

There has been some recent speculation that the frequency of Down syndrome and other birth abnormalities varies seasonally. Since genetic traits do not exhibit seasonality, this provides indirect evidence that environmental influences play a causal effect [(3)].

The prevalence and structural features of CHD in DS, as well as the associated consequences and causes of morbidity and mortality, must be known in order to include preventative efforts and improve the quality of life of the patient in a specific environment. Furthermore, early detection of cardiac problems is crucial for the best chance of survival because the kind and timing of CHD might alter the prognosis. There is a dearth of reliable data from African countries, as well as an issue with regional variation around the world, which hinder our capacity to make informed decisions [(4)].

There are numerous congenital deformities associated with Down syndrome, including heart problems and digestive system abnormalities. Primary (or thyroid) hypothyroidism and autoimmunity are two of the most common conditions in patients with Down syndrome. Patients with DS are more likely to have subclinical hypothyroidism, when the TSH level is just slightly elevated. Compared to non-Down syndrome neonates, Down syndrome infants have a slightly higher rate of TSH and lower levels of T4 [(5)].

A hypothalamic-pituitary-thyroid axis abnormality or a mild form of congenital hypothyroidism unique to the thyroid has been hypothesised in DS. Thyroxine therapy in children with DS was thought to improve psychomotor development in the first two years of life, based on the hypothesis that young children with DS have a moderate form of congenital thyroid hypothyroidism [(5)].

We aimed at this study to assess thyroid function abnormalities in children with Down syndrome and congenital heart disease.

SUBJECTS AND METHODS
From April 2019 throughout October 2019, at Cardiology Unit of Pediatric and Neonatology Department at Zagazig University Hospitals, our cross-sectional trial was conducted on 50 subjects CHD-affected patients diagnosed with DS.

Ethical consent:
When all parents of participants completed informed permission papers and submitted them to the research ethics committee at Zagazig University, the study was permitted (ZU-IRB#6421). Ethics guidelines for human experimentation were adhered

Received: 21/12/2021
Accepted: 20/02/2022

to in line with the Helsinki Declaration of the World Medical Association.

Inclusion criteria: CHD-affected patients diagnosed with DS (with or without chromosomal studies).

Exclusion criteria: Patients with serum tetraiodothyronine (T4) and/or free tetraiodothyronine (FT4) and/or triiodothyronine (T3) changed by age and/or clinical hypothyroidism and leukemia and/or non-cardiogenic factors that could affect the weight and height gain.

All participants of the study were subjected to:

A) Complete history taking.

B) Complete Clinical examination including:

The medical records contained the following DS-related phenotypic clinical features: There was a projecting tongue and an epicanthic fold on the upper eyelids of mongoloid individuals. They also had brachycephaly and a depressed nasal bridge. In addition to gender, age of diagnosis, and the mother's age at delivery, demographic information was gathered. Referred patients were evaluated clinically for signs and symptoms such as fatigue, cold intolerance, constipation, dry skin and hair, as well as myxedema, bradycardia, chilly peripheries, and sluggish tendon reflexes. Weight and length were measured using a stadiometer, and centile positions were reported using growth charts drawn from the work of **Cremers and colleagues [6].**

C) Imaging:

Plain chest X-ray: View from the posterior-anterior angle to look for cardiomegaly as well as other cardiovascular conditions.

Echocardiography: Transthoracic echocardiography was performed on all CHD patients using a commercially accessible device (Acuson Sequoia Ultrasound System C512, Acuson, Mountain View, CA). Two pediatric cardiologists with experience in digital imaging were blinded to the findings of the serum tests when they inspected the digitally captured images.

D) Laboratory investigations:

Thyroid function parameters:

Plasma TSH was measured with an electrochemiluminescence immunoassay.

Plasma FT3 and FT4 were measured with an electrochemiluminescence immunoassay (E170, Roche Diagnostics).

Chromosomal analyses: The Giemsa-Trypsin banding method was used at the medical genetics laboratory to analyse blood cells.

Statistical analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for the Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Numbers and percentages were used to represent qualitative data. Mean ± standard deviation (SD) were used to represent quantitative data. Different qualitative factors were examined using the Chi square (X^2) test. T-test and one-way ANOVA test were used to compare 2 or 3 groups respectively as regard quantitative data. P value of 0.05 was considered significant and of 0.001 was considered highly significant.

RESULTS

Table (1) shows the demographic and diagnostic data of the study group. Atrial septal defect (ASD) - Ventricular septal defect (VSD) were the most prevalent diagnosis by a percent of 52%.

Table (1): Demographic and diagnostic data of the study group (n=50)

Variable	Frequency (N=50)	Percentage (%)
Gender		
Male	29	58.0
Female	21	42.0
Age		
Mean ± SD	6.7±2.1	
Type of congenital heart		
Cyanotic Acyanotic	19 31	38.0 62.0
Diagnosis		
VSD-ASD	26	52.0
PDA	3	6.0
PDA-VSD	2	4.0
Fallot (TOF)	8	16.0
Transposition of great vessels with atrial septostomy	7	14.0
Tricuspid atresia	4	8.0

Figure (1) shows that 10% of cases had congenital hypothyroidism.

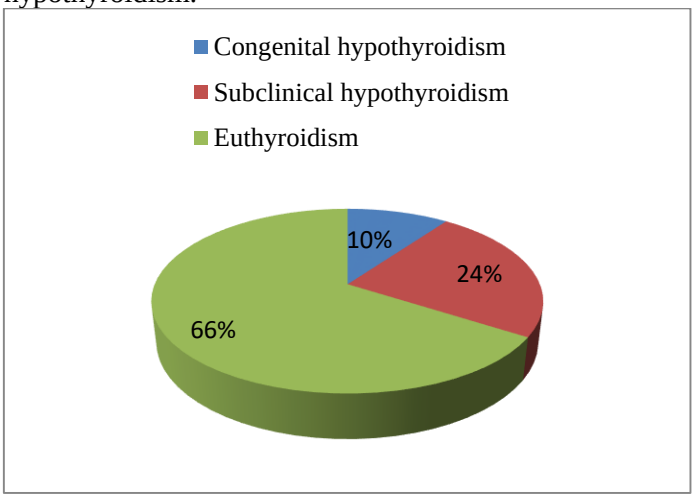

Figure (1): Distribution of cases according to thyroid function

Figure (2) shows that 88% of cases have trisomy +21 on karyotyping.

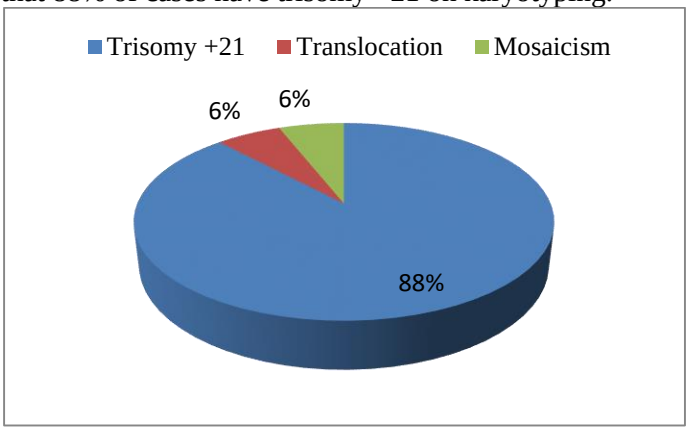

Figure (2): Distribution of cases according to karyotyping of Down cases

Table (2) shows that type of congenital cardiac defect is not associated with thyroid function.

Table (2): Relation between thyroid function and type of congenital heart disease

Variable	Cyanotic			Acyanotic			T test	P value
TSH	3.0	±	1.0	3.2	±	1.01	0.682	0.498
FT4	16.1	±	3.3	16.0	±	3.1	0.108	0.914
FT3	2.2	±	0.61	2.4	±	0.72	1.008	0.318

(Table 3) shows that there was high significant difference between the studied groups as regard TSH, FT4 and FT3 levels while there was no statistically significant difference between them as regard age or gender.

Table (3): The characteristics of 50 patients with Down syndrome according to thyroid status

Variable	Congenital hypothyroidism N=5			Subclinical hypothyroidism N=12			Euthyroidism N=33			F	P value
Age	6.6	±	1.2	6.7	±	1.3	6.6	±	1.8	0.091	0.045
TSH	4.2	±	1.0	3.3	±	0.2	2.3	±	0.3	10.21	**<0.001**
FT4	9.1	±	2.0	10.9	±	2.2	15.9	±	3.3	16.75	**<0.001**
FT3	1.4	±	0.22	2.2	±	0.1	3.8	±	0.32	262.8	**<0.001**
	Congenital hypothyroidism N=5			**Subclinical hypothyroidism N=12**			**Euthyroidism N=33**			χ^2	**P value**
	N		%	N		%	N		%		
Gender											
Male	3		60.0	7		58.3	19		57.6		
Female	2		40.0	5		41.7	14		42.4	0.011	0.994

Table (4) shows that thyroid health and maternal age were highly statistically related.

Table (4): Relation between thyroid status and maternal age

Variable	Congenital hypothyroidism N=5			Subclinical hypothyroidism N=12			Euthyroidism N=33			F	P value
Age	32.6	±	3.1	29.7	±	2.1	26.6	±	1.8	25.27	**<0.001**

Table (5) shows that genetic variants of Down syndrome have no major impact on thyroid function.

Table (5): Relation between genetic types of Down syndrome and thyroid function

Variable	Trisomy +21 N=44			Translocation N=3			Mosaicism N=3			F	P value
TSH (uIUL/ml)	3.4	±	0.1	3.3	±	0.3	3.1	±	0.11	0.113	0.892
FT4 (ng/dl)	11.3	±	2.3	11.1	±	2.1	11.2	±	2.0	0.006	0.993
FT3 (ug/dl)	2.5	±	0.32	2.6	±	0.21	2.7	±	0.42	0.649	0.52

DISCUSSION

Down syndrome is the most frequent, life-compatible chromosomal anomaly, occurring in between 1/700 and 1/1800 live births [7]. The clinical symptoms of DS, particularly in neonates, vary widely across people, but the diagnosis is based on its typical characteristics and linked functional and systemic abnormalities. In 16 to 62 percent of people with DS, congenital heart disease, the most serious systemic abnormality, is present. A person's quality of life and mortality are linked to the severity of congenital heart disease (CHD), even though it's a common underlying cause of DS [8].

Thyroid disorder, particularly subclinical hypothyroidism, is more common in people with DS. An SH-related loss of heart function in DS children will increase their clinical state and potentially influence their lifespan [9]. Having DS has also been linked to increased baseline TSH rates, even in the absence of thyroid disease, according to several studies. This is thought to be the result of a DS-specific TSH-setting malfunction [10]. Detecting thyroid disease in patients with DS is difficult, and serologic monitoring is suggested. For children under the age of one year, the American Academy of Pediatrics recommends routine thyroid screenings at six months and one year of age [11].

The present study included 50 children with trisomy 21 and CHD, 58% of cases were males and 42% were females, the mean age was 6.7±2.1 years, 38% of cases were cyanotic heart disease and 62% were acyanotic, ASD was the most prevalent diagnosis representing 52% of cases.

Yadav *et al.* [12] at The Northeast India tertiary treatment facility did a cross-sectional case control study. Children and adolescents over the age of 7 with subclinical hypothyroidism and a TSH greater than 7.5 mIU/L were included in the study. For this study, 27 children and adolescents aged 11 to 17 years old were eligible for inclusion. Twenty euthyroid children and adolescents, matched for age, gender, and height, were recruited as controls. Each member had a common hometown or city with the others.

Our study verified that 10% of cases were congenital hypothyroidism, 24% were subclinical hypothyroidism and 66% were euthyroidism. **Pascanu *et al.*** [13] studied 63 DS children and found that 39 (62%) had normal thyroid function, while 24 (38%) had thyroid hormones that were altered. There was only one case with chronic primary congenital hypothyroidism, however in 23 patients, a high TSH with a normal FT4 was found (subclinical hypothyroidism).

We also found that 88% of cases had trisomy +21 on karyotyping, 6% had translocation, and 6% had mosaicism. In the study of **Mihci *et al.*** [9] trisomy +21 was found in 91.98 percent of cases, 3.74 percent of translocations, 3.74 percent of mosaicisms, and 0.53 percent of cases with 21 del 19 p.

In the present study, there was no significant relation between thyroid function and the type of congenital heart disease. **Lee *et al.*** [14] agreed with us when they verified no significant relation between cyanotic heart and abnormal thyroid function. This is consistent with **Toscano *et al.*** [15] who showed no abnormalities in myocardial structure or function in Down syndrome (DS) children with subclinical hypothyroidism (SH).

In the present study, we noticed highly significant differences between the different thyroid states as regard TSH, FT4 and FT3 levels, but found no statistically significant differences between them as regard age or gender. **Mihci *et al.*** [9] agreed with us when they reported a highly significant relation between the studied different thyroid states and TSH, FT4 and FT3 levels.

We also found a highly significant relation between thyroid status and maternal age. This came in agreement with **Dayal *et al.*** [16] as the records of patients with congenital hypothyroidism (CH) caused by thyroid dysgenesis (TD) at the Chandigarh Pediatric Endocrinology Clinic at the Advanced Pediatric Center in Northwest India were reviewed retrospectively between 2004 and 2014. These patients had considerably older mothers (25.87± 4.17 years) as compared to the reference group's 23.87 ±3.34-year-old mothers (p 0.0001) when looking at the relationship between maternal age and child thyroid function.

CONCLUSION

Thyroid dysfunction, most commonly subclinical hypothyroidism, is frequent in children with DS, with no relation to length, weight, maternal age or sex with thyroid function.

Conflict of interest: The authors declare no conflict of interest.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution: Authors contributed equally in the study.

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