Curr Pediatr Res2021; 25 (11): 1070-1075 *ISSN 0971-9032*
www.currentpediatrics.com

Thyroid function test in children with down syndrome.

Matheel Taqi Alzubaidi*, Ghufran Mahdi Abdulhadi, Jasim Mohammed Hashim

Department of Pediatric, College of Medicine, University of Karbala, Kerbala, Iraq

Abstract

Background: Down Syndrome (DS) is the common genetic cause of moderate intellectual disability. DS have an increased incidence of Congenital Heart Disease (CHD), gastrointestinal anomalies, endocrine dysfunction of which thyroid dysfunction are the most common.
Aim: Assessment of the changes in Thyroid Function Test (TFT) among a group of phenotypically DS children and compare it with a small group of the age-matched general population.
Methods: This case-control study included measurement of TFT in a small group of children with DS who visited Al-Zahra teaching hospital for different complaints and compared to TFT in age-matched seems to be healthy children who visited the outpatient clinic of Al-Zahra teaching hospital as a control group.
Results: Thirty-four children aged 5 days to 9 years with phenotypical features of DS were included in this study, 8 (23%) of them had hypothyroidism with subclinical hypothyroidism in most of them (6 children), 3 (8%) of them had hyperthyroidism and 2 (5.8%) had thyroid hormone resistance. We also found a statistically significant difference in TFT between DS children and the general population. The study also showed that Thyroid-Stimulating Hormone (TSH) level is higher and Thyroxin (T4) level is lower in DS children who had other associated anomalies like CHD compared to children without such anomalies, but it was statistically not significant.
Conclusion: DS children had a high frequency of thyroid dysfunction with subclinical hypothyroidism was the common finding.

Keywords: Down syndrome children, Hypothyroidism, Subclinical hypothyroidism.

Accepted on 23rd November, 2021

Introduction

Down syndrome

Approximately 1 in 733 of the live births had trisomy 21, which represent the most common genetic cause of moderate intellectual disability [1]. In 1866, John Langdon Down, a British physician, published an article entitled “Observations of an ethnic classification of idiots”.

He described some of the common associated physical features of individuals whom we now consider to have DS: mental retardation, hypotonia, CHD, abnormalities of the digestive tracts, congenital cataracts, and abnormalities of the face, and hands [2]. The primary risk factor for DS is maternal age.

The chances of a woman having a child with DS increase with age because older age has a higher risk of improper chromosome division [3].

Clinical features

The phenotypic pattern of DS is characteristic and consistent enough to allow recognition of an affected neonate [4]. In most instances DS is recognizable at birth by the craniofacial features; the head circumference is small with a brachycephalic skull, sloping upwards of the palpebral fissures and marked epicanthic folds.

The ears may be small with an over folding helix. The tongue seems large protrude because the mouth is relatively small [5]. Later on moderate to severe learning difficulties, hearing impairment from otitis media, visual impairment from cataracts, myopia, squints, increased risk of solid tumours and leukaemia, increased risk of atlantoaxial instability, increased risk of thyroid dysfunction and coeliac disease, epilepsy, delay development and cognitive impairment.

The life expectancy for children with DS is reduced and is approximately 50-55 years [6,7].

Thyroid hormone

Thyroxine (T4) is the major hormone secreted by the thyroid gland which is converted to Triiodothyronine (T3) to exert its effects. While 20% of circulating T3 is secreted by the thyroid [8].

Extrauterine thyroid adaptation

In the second trimester, the hypothalamic-pituitary-thyroid axis becomes functional. While in the third trimester, the peripheral metabolism of thyroid hormones become mature [9]. The conversion from the fetal state of thyroid hormone inactivation to a state of relative thyroidal hyperactivity must be started at the time of delivery, in which there is an increase in circulating T4 and T3 levels due to the abrupt increase in hypothalamic TRH stimulating pituitary TSH secretion.

The cold-stimulated TRH-TSH surge is short-lived) TSH concentrations decrease progressively to normal infant levels

by 3 to 5 days ([1,10]. TSH, T4, and T3 do not cross the placenta in significant amounts. Fetal serum concentrations primarily reflect fetal secretion and metabolism [8].

Interpretation of thyroid function test

- If the TSH level is high and the T4 result is low this suggests an under-active thyroid (hypothyroidism).
- If the TSH level is low and the T4 result is high this suggests an over-active thyroid (hyperthyroidism).
- If the TSH level is slightly raised but the T4 level is still within the normal reference range this is called subclinical hypothyroidism or mild thyroid failure.
- A low TSH with a low FT4 may be a result of a failure of the pituitary gland (secondary hypothyroidism) or a response to a significant non-thyroid illness [11].

Thyroid dysfunction in down syndrome

Hypothyroidism: Hypothyroidism is much more common than hyperthyroidism, present after birth, acquired during childhood or adolescence, may be symptomatic or asymptomatic [12].

Congenital hypothyroidism: Congenital Hypothyroidism (CH) is the most common endocrine disorder observed in newborn infants [13].

Clinical manifestations

Infants are usually asymptomatic at birth. This may be due to partial transplacental passage of maternal T4. During the neonatal period and early infancy Symptoms and signs are vague, nonspecific, prolonged physiological jaundice, with an unconjugated hyperbilirubinemia, feeding difficulties, inactivity, macroglossia, constipation, wide fontanels, dry and mottled skin, hypothermia, and hoarse cry should arouse suspicion. [14,15].

The examination may reveal the presence of coarse facies, umbilical hernia, oedema of genitals and extremities, cardiomegaly, and bradycardia [16].

Diagnosis: Ten per cent to 15% of infants with congenital hypothyroidism have T4 values in the normal range (7-10 μg/dL, or 90-127 nmol/L). The diagnosis is made when serum measurements of T4 and/or free T4 (FT4) and Thyroid-Stimulating Hormone (TSH) concentrations. In the neonatal period (2-6 weeks), serum T4 <84 nmol/L (6.5 μg/dL), FT4 <10 pmol/L (0.8 ng/dL), and TSH >10 mU/L (10 uIu/mL) go with congenital hypothyroidism [4]. Radiography may show Retardation of osseous development at birth [1].

Treatment: The treatment of choice is Levothyroxine (L-T4). The initial starting dose is 10-15 μg/kg/day orally. Monitoring of serum Levels T4 or FT4 and TSH at intervals (every 1-2 months in the 1st 6 months of life, and then every 2-4 months between 6 months and 3 years of age) [17,18].

Hyperthyroidism: Incidence of hyperthyroidism less commonly in children than hypothyroidism [19]. This usually results from graves', secondary to the production of thyroid-stimulating immunoglobulins. The clinical features are similar to those in adults, like anxiety, restlessness, increased appetite, sweating, diarrhea, weight loss, rapid growth in height, advanced bone maturity, tremor, tachycardia, goitre (bruit), learning difficulties/behavior problems although eye signs are less common. It is most often seen in teenage girls [20].

Patients and Methods

Study time and location

A study was conducted in Al-Zahra teaching hospital in Al-Najaf and Al-Ashraf from 1st September 2016 to 26th of January 2017.

Thirty-four children were diagnosed with DS based on characteristic clinical features of up slanting palpebral fissure, brachycephaly, hypotonia, brachydactyly, sandal gap, single simian crease, and who were visiting the hospital for different complaints like shortness of breath, diarrhea and fever were enrolled in this study.

Study design

A case-control study which were including socio demographic data, symptoms of thyroid dysfunction, any associated anomalies, thyroid function test.

After consent was taken from their parents, a thyroid function test was done for them. A small group of age-matched seems to be healthy children who visited the outpatient clinic of Al-Zahra teaching hospital for simple acute illness were selected as a control group.

Serum or plasma was collected in a tube with separator gel that freezes at -25, then allowed to thaw at room temperature, then T4, TSH levels were measured using an automated quantitative test for immune enzymatic determination of these hormones in human serum using the ELFA technique (Enzyme-Linked Fluorescent Assay) using minividas (bioMerieux diagnostic).

Follow-up thyroid function test done in 4 children with DS whose initial screen was done in the early neonatal period and repeated at infancy.

Study population

There were 14 male, 20 female children with DS aged from 5 days to 9 years. With 17 males, 18 females aged from 9 days to 9 years as a control group. 0n the base of these investigations the patients were classified as euthyroid, hypothyroid, hyperthyroid, and thyroid hormone resistance (Table 1).

Tests	Age	Reference range
T4	0-3 days	103-258 nmol/L
	3-30 days	64-193 nmol/L
	31-365 days	77-180 nmol/L
	1-5 years	58-142 nmol/L
	6-18 years	58-129 nmol/L
TSH	0-3 days	1.0-20.00 μIU/L
	3-30 days	0.50-6.50 μIU/L
	1-5 months	0.5-6.0 μIU/L
	6 months-18 years	0.5-4.5 μIU/L

Table 1. The reference range for T4, TSH level [1].

Statistical analysis

Statistical analysis was carried out using SPSS version 20. Categorical variables were presented as frequency and percentage. A p-value ≤ 0.05 was considered statistically significant.

Results

Thirty-four children with DS were included in this study, 20 (58.8%) of them were female, 14 (41.1%) were male. (60%) of them were younger than one year. The study also includes 35 children who were age and sex-matched, apparently healthy who visiting the outpatient clinic of Al-Zahra hospital as the control group.

Twenty-two of children with DS had other associated anomalies like CHD like VSD in 8 (36%), complete AV canal in 5 (22%), multiple CHD in 3 (8.8%), celiac disease in 1 (4.5%) and duodenal atresia in 1 (4.5%) of studied DS children (Table 2).

Parameter	Patients	Control	p-value
Age	5 days-9 years	9 days-9 years	0.424
	28.4 ± 30.2 months	23.08 ± 25.5 months	
Sex: male	14 (41.1%)	17 (48.5%)	0.544
Sex: Female	20 (58.8%)	18 (51.4%)	
Symptoms of thyroid dysfunction	Zero	Zero	
Associated anomalies	22	Zero	
Maternal age	30.11 ± 6.08 years	27.45 ± 6.84 years	0.102

Table 2. Show demographical features of patients and control.

Eight (23%) of totally 34 DS children included in our study had laboratory evidence of hypothyroidism, 6 of them were subclinical hypothyroidism which is defined as normal T4 and elevated TSH, one child was congenital hypothyroidism as evident by low T4, high TSH value at 4 months age. the other has central hypothyroidism as defined by low T4 and normal TSH. Three (8%) of them had hyperthyroidism and 2 (5.8%) had thyroid hormone resistance as defined as elevated both T4 and TSH levels, as shown in Table 3.

Diagnosis	Frequency	T4 (Mean+SD)	TSH (Mean+SD)
Euthyroid	21 (61.7%)	106.10 ± 21.20	2.82 ± 1.51
Hypothyroidism	8 (23%)	96.47 ± 24.06	13.09 ± 9.69
Hyperthyroidism	3 (8%)	231.54 ± 55.37	2.34 ± 0.65
Thyroid hormone resistance	2 (5.8%)	175.83 ± 35.05	8.43 ± 1.59

Table 3. Show the frequency of abnormalities in TFT among DS children.

The study showed a statistically significant difference in thyroid function test between patients and control group, as shown in Table 4.

		N	Mean	Standard Deviation	P-value
T4	Patients	34	119.0106	46.84451	0.004
	Control	35	94.0766	14.98445	
TSH	Patients	34	5.5344	6.42897	0.006
	Control	35	2.3737	1.22721	

Table 4. Shows thyroid function test in down syndrome and control.

There is also no statistically significant difference in TFT between male and female children with DS as shown in Table 5.

	Sex	N	Mean	Standard Deviation	P-value
T4	male	14	132.5493	62.31519	0.162
	female	20	109.5335	30.41091	
TSH	male	14	3.6614	2.10404	0.158
	female	20	6.8455	8.02267	

Table 5. Show thyroid function tests in males and females with down syndrome.

Also, the study showed statistically no significant difference in TFT in DS children between those who had other associated anomalies like CHD and those who do not as shown in the following Table 6.

		N	Mean	Standard Deviation	P-value
T4	anomaly	22	113.0295	49.80583	0.321
	no anomaly	12	129.9758	40.5559	
TSH	anomaly	22	6.5309	7.4994	0.226
	no anomaly	12	3.7075	3.31644	

Table 6. Shows thyroid function test in children with or without associated anomalies.

Regarding thyroid function test between different ages in DS children, there is statistically no significant difference as shown in Table 7.

		N	Mean	Standard Deviation	P-value
T4	Beyond infancy	20	119.85	41.98	0.903
	Infancy	14	117.8	54.69	
TSH	beyond infancy	20	4.14	3.58	0.134
	Infancy	14	7.52	8.88	

Table 7. shows thyroid function test in children with or without associated anomalies.

Discussion

Down syndrome is a commonest chromosomal disorder, so a lot of studies were conducted about different associated anomalies and one of them is thyroid hormones dysfunction which has a great impact on their life because thyroid hormones affect most body systems especially neurological development which is already impaired in children with DS. In this study, there is no statistically significant difference in age and gender between DS children and the control group. Also, there is no difference in maternal age between patient and control group although the mean maternal age for DS children was 30 years which is older than the control group. While in Lalaine et al. study was 34.23 years when hypothyroidism was diagnosed [21].

In our study hypothyroidism was present in 8 (23%) of a total of 34 patients which is higher than Pueschel et al. study in which hypothyroidism was present in 16% of children with DS

[22]. While Rubello et al. study showed the prevalence of subclinical hypothyroidism in 32.5% of DS children which is higher than our study due to larger sample size [23]. In the Shaw et al. study, which was conducted in Nepal in 2006 on 32 children with DS showed hypothyroidism in 15.6% of studied patients, most of them were subclinical hypothyroidism [24]. While an Italian series conducted by Colombo et al. in 1992 with a mean age of five years found 3.6% of children was hypothyroidism [25]. In this study 3 (8%) of the patient had hyperthyroidism as evident by elevated T4 level but with normal TSH, this was also found in Audrey et al. study which shows hyperthyroidism in 7% of patients [25]. while in Kevalee et al. study, hyperthyroidism was present in 2.1% of DS in the study [26].

In our study, there was one case (2.9%) congenital hypothyroidism as evident by low T4 (105 69 nmol/L) and high TSH (25 18 μIU/L) which measured at 5 days and 4 months respectively, as apposite to Tuysuz et al. The study which found 1.8% of studied patient had congenital hypothyroidism, where the sample size was 320 children with DS aged 5 days to 10 years while in our study because small sample size less neonate included in this study [27]. When we compare TSH between children with DS and the control group there is a statistically significant difference between the two groups as TSH Mean ± SD was 5.53 ± 6.42 which is significantly higher as compared to TSH in the control group as the mean TSH level was 2.37 ± 1.22 with more risk of hypothyroidism whether congenital or acquired in DS children. This is also evident in Ira et al. in their study, which revealed T4 concentrations in children with DS were significantly lower, and TSH higher than those in the general population when conducted on 159 neonates with DS [28]. The same result was also found in the Sudanese study which shows a significant increase in TSH level in DS children compared to the control group [29].

In our study, although serum T4 level is significantly different in DS compared to the general population it was in an upper limit of reference range indicating some element of thyroid hormone resistance. Supporting this possibility the presence of 2 children with thyroid hormone resistance with elevated both T4, TSH with Mean ± SD (175.83 ± 35.05), (8.43 ± 1.59) respectively. This is mostly attributed to a different gene mutation in children with DS because of the extra copy of chromosome 21 or part of it [9].

In this study, there were higher serum levels of TSH and lower levels of T4 in DS females as compared with a male but with no statistically significant difference as Cebeci et al. study showed [30]. Also, there was a higher TSH level and lower T4 level in DS children who had other associated anomalies like CHD compared to children without such anomalies, but it was statistically not significant, although 9 out of totally 13 DS children who had thyroid dysfunction also had other associated anomalies.

There was no statistically significant difference in T4, TSH levels between infancy and beyond the infancy age group. but during follow up investigation of T4, TSH level which was done for 4 children with DS show a decrease in T4 and TSH level with advancing age as an initial test done during the neonatal period then a few months later this support Claret et al study which shows that subclinical hypothyroidism can resolve spontaneously without treatment in >70% of patients [31].

Conclusion

Down syndrome children had a high frequency of thyroid dysfunction with subclinical hypothyroidism was the commonest finding, with higher TSH level than the general population.

Recommendation

- Measurement of thyroid function test during the early neonatal period in Down syndrome children then subsequently according to initial TFT result.
- Selection of larger samples of children with Down syndrome for assessment of TFT.

References

1. Kliegman RM, Stanton BF, Geme JW, et al. Nelson textbook of pediatrics. (20th edn) Elsevier 2016.
2. Holmes LB. Common malformations. Oxford University Press 2012; 49-50.
3. Moore L, Bradlee M, Singer M, et al. Chromosomal anomalies among the offspring of women with gestational diabetes. Am J Epidemiol. 2002; 155(8): 719-24.
4. Rudolph CD, Rudolph AM, Lister GE, et al. Rudolph's pediatrics. (22nd edn) McGraw-Hill Companies 2011; 1576.
5. Michael AP, McIntosh N, Helms PJ, et al. Forfar and Arneil's textbook of pediatrics. (7th edn) Elsevier 2008; 386-7.
6. Read A, Donnai D. The New Clinical Genetics. (2nd edn) Scion 2010.
7. Bull MJ, Committee on Genetics. Health supervision for children with down syndrome. Pediatr 2011; 128(2): 393-406.
8. Heuer H, Visser T. Minireview: Pathophysiological importance of thyroid hormone transporters. Endocrinology 2009; 150(3):1078-83.
9. Marcdante KJ, Kliegman RM. Nelson essentials of pediatrics. (7th edn) Elsevier 2015; 596-601.
10. Dumitrescu AM, Liao XH, Best TB, et al. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. Am J Hum Genet 2004; 74(1): 168-75.
11. https://www.btf-thyroid.org/thyroid-function-tests
12. Kaplowitz PB. Subclinical hypothyroidism in children: Normal variation or sign of a failing thyroid gland. Int J Pediatric Endocrinol 2010; 281453.
13. Elzouki AY, Harfi HA, Nazer HM, et al. Textbook to clinical pediatrics. (2nd edn) Springer 2012; 3767-77.

14. Balhara B, Misra M, Levitsky LL. Clinical monitoring guidelines for congenital hypothyroidism: Laboratory outcome data in the first year of life. J Pediatric 2011; 158(4): 532-7.
15. Leger J, Olivieri A, Donaldson M, et al. European society for pediatric endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. J Clin Endocrinol Metab 2014; 99(2): 363-84.
16. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. Orphanet J Rare Dis 2010; 5: 17.
17. Grüters A, Krude H. Detection and treatment of congenital hypothyroidism. Nat Rev Endocrinol 2011; 8(2): 104-113.
18. Zeitler P, Solberg P. Pharmacy and therapeutics committee of the Lawson Wilkins pediatric endocrine society: Food and levothyroxine administration in infants and children, J Pediatric 2010; 157(1):13-14.
19. Popova G, Paterson WF, Brown A, et al. Hashimoto's thyroiditis in down's syndrome: Clinical presentation and evolution. Horm Res 2008; 70: 278-284.
20. Sperling M. Pediatric endocrinology. (3rd edn) Elsevier 2011.
21. Audrey L, Matitu U, Estrada C. Prevalence of thyroid disorders among children with down syndrome. Int J Pediatr Endocrinol 2015; P101.
22. Siegfried MP, Jackson IM, Giesswein P, et al. Thyroid function in down syndrome. Res Dev Disabil 1991; 12(3): 287-96.
23. Rubello D, Pozzan GB, Casara D, et al. (1995). Natural course of subclinical hypothyroidism in Down's syndrome. Journal of Endocrinol Invest 1995;18(1): 35-40.
24. Shaw CK, Thapalial A, Nanda S, et al. Thyroid dysfunction in down syndrome. Kathmandu Univ Med J 2006; 4(2): 182-6.
25. Colombo O. Thyroid dysfunction in down syndrome: A review. Down Syndr Res Pract. 1994; 2(3): 112-5.
26. Kevalee U, Tanpaiboon P, Pongprot Y, et al. Thyroid Functions in Children with down's syndrome. J Med Assoc Thai 2008; 91 (1): 56-61.
27. Tüysüz B, Beker DB. Thyroid dysfunction in children with down's syndrome. Acta Paediatr 2001; 90(12): 1389-93.
28. Erlichman I, Mimouni FB, Erlichman M, et al. Thyroxine-based screening for congenital hypothyroidism in neonates with down syndrome. J Pediatr. 2016; 173: 165-8.
29. Bahar GM, Modawe GA, Ahmed SA, et al. Assessment of thyroid hormones in Sudanese patients with down. Pyrex J Biomed Res 2015; 1(5): 42-44.
30. Cebeci AN, Güven A, Yıldız M. Profile of Hypothyroidism in down syndrome. J Clin Res Pediatr Endocrinol 2013; 5(2): 116-20.
31. Cristina C, Albert G, David B, et al. Subclinical hypothyroidism in the first years of life in patients with Down syndrome. Pediatr Res. 2013; 73(5): 674-8.

*Correspondence to:

Matheel Taqi Alzubaidi

Department of Pediatric

College of Medicine

University of Karbala,

Kerbala, Iraq

Email: alaaj.nasrawi@uokufa.edu.iq