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THYROID DYSFUNCTION IN LIBYAN CHILDREN WITH DOWN SYNDROME

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ABSTRACT

Background: Down syndrome (DS) is the most common chromosomal abnormality observed in live born infants. Individuals with DS exhibit a wide range of thyroid dysfunction. In this study, we aimed to document the range of thyroid function in a cohort of Libyan children with DS. **Patients & Methods:** Observational descriptive study were conducted at 2 centers in Libya (Tripoli Medical Centre, and Al-Thawra hospital) between (2011 – 2018). 183 Libyan children with down syndrome (DS) who were admitted to pediatric department of the 2 centers. Information on age, gender, maternal age at childbirth, presence of congenital anomalies, family history of thyroid disorders, and complete TFTs were obtained and others associated disorder. **Results:** 183 children with DS were participated in the current study, aged between [5 days – 16 years], there was a slight female predominance (55%). Of the total of 183 DS children, TFTs were normal in 107 children (58%), and were found to be abnormal. In 76 (42%). (30%) have overt thyroid diseases. Overt thyroid diseases including CH (1%), acquired hypothyroidism 83%), and hyperthyroidism (4%), while SCH was found in more than two third of cases (70%) or (53 out of 76 cases). Of 53 cases with SCH, 35 cases showed a spontaneous decrease of TSH to normal level, 10 patients showed persistently elevated TSH level, and thyroxin therapy was started for them, while 8 cases showed fluctuation in TSH level. **Conclusion:** Thyroid dysfunction is common among Libyan children with DS. SCH represented more than two-third of the thyroid dysfunction in this study. No significant correlation have seen in this study between thyroid dysfunction in children with DS and the presence of congenital anomalies as well as no significant correlation between thyroid dysfunction in DS children and maternal age, in contrast; we have observed a highly significant correlation between thyroid dysfunction in DS children and positive family history of thyroid dysfunction.

KEYWORDS: Children with DS, Thyroid dysfunction, hypothyroidism, SCH, CH.

ABBREVIATION

DS: Down Syndrome, CH: Congenital Hypothyroidism, SCH: Subclinical, Hypothyroidism, TFTs: Thyroid Function Tests.

INTRODUCTION

Down's syndrome (DS) is one of the most common survivable chromosomal syndromes,[1] caused by the presence of a 3rd copy of the whole, or a critical part, of chromosome 21 (trisomy 21). Global live-birth rates for DS range between 1.5/1000 (1 in 660 infants) and 1.2/1000 (1 in 826 infants),[2,3] with no predilection for race or socioeconomic group.[4] DS children are characterized by typical dysmorphic features, associated with an increased incidence of certain medical complications, they are more likely to occur with advanced maternal age and has an increased prevalence of autoimmune disorders affecting both endocrine and non-endocrine organs.[5,6] There is an intriguing association between DS and thyroid abnormalities, which include sub-clinical and overt hypothyroidism, hyperthyroidism, and positive thyroid antibodies, the prevalence of these abnormalities is varied, depending on the diagnostic criteria, laboratory techniques and the selected population which includes sample size and age group.[5] In general, thyroid disorders have been reported to have a prevalence of 3 - 54% in people with DS, with the frequency of thyroid dysfunction increasing with age.[7] It is estimated that the lifetime prevalence of hypothyroidism in DS is 30 -50%.[8] Individuals with DS are at an increased risk of developing thyroid disease, primarily autoimmune, with a life time prevalence ranging from 13% to 63%.[9] The prevalence of hypothyroidism in DS is higher than that of hyperthyroidism, and increases with age,[5] hyperthyroidism, although rarer, also occurs more frequently in DS individuals than in the general population.[7] SCH is the most common form of thyroid

dysfunction in DS, being reported in 25 - 32% of patients.[10, 11] There are a few reasons for the lack of consensus surrounding the management of SCH. Firstly, there is a paucity of data on the natural history of SCH in normal children, the concern is that, if left untreated, SCH would progress to overt hypothyroidism. As there is also a paucity of data derived from patients with DS, pediatricians currently draw data from studies on normal children and normal adults, which may not be applicable to children with DS. Secondly, there are no large pediatric randomized controlled studies comparing outcomes in patients with SCH who were treated with thyroxine and those left untreated. Again, most clinicians rely on data from adult studies, which may also produce conflicting recommendations. Many of the published guidelines only support treatment with thyroid hormone for patients with DS where the TSH level is greater than 10 µIU/l. Most, such as those from the UK, do not support thetreatment of SCH when a TSH level is less than 10 µIU/l with normal FT4 values.[12]

The prevalence of congenital hypothyroidism is recognized to be considerably higher in newborns with DS than in general population,[13] some authors[14] find the evidence for this very unconvincing because thyroid dysgenesis (ectopy or agenesis which account for 85% of cases of CH is not more frequent in DS and the coexistence of DS with severe persistent primary CH with a normally located gland of normal or increased size (dyshormonogenesis) may represent a chance association. Instead, in children with DS mild plasma TSH elevation is extremely prevalent in early infancy.[15,16]

Infants with DS have a greater prevalence of compensated hypothyroidism during the 1st few months.[7,17,18,19] The natural progression of compensated hypothyroidism includes conversion to euthyroid or primary hypothyroidism state.[10,13,15] Beyond the newborn period, the incidence of elevated TSH values in DS increases and has been reported to be as high as 85% of infants under the age of 12 months.[20]

The clinical manifestations of hypothyroidism, and other thyroid disorders are nonspecific and may be attributed to the DS itself. Diagnosis based solely on clinical features is therefore unreliable, and laboratory findings that confirm diagnosis are essential. Early detection and treatment of Hypothyroidism are essential, in order to maximize cognitive abilities in this already impaired population.[7]

This study was conducted at pediatric departments of 2 centers in Libya (Tripoli Medical Center and Al-Thawra hospital), it aimed to document the range of thyroid function in a cohort of Libyan children with DS.

Al-Thawra hospital, Albyida city (is a city located in the Eastern part of Libya). Tripoli Medical Center, Tripoli (is the capital of Libya, and located in the Western part of the country).

PATIENTS AND METHODS

This is an observational study was conducted at 2 centers in Libya, on children with DS between (2011 – 2018).183 Libyan children who were admitted to the pediatric departments of 2 centers. All children included in this study, had clinical characteristics of DS, and few of them confirmed by cytogenetic studies. Information on age, gender, maternal age at childbirth, presence of congenital anomalies, family history of thyroid disorders, and complete TFTs were obtained. Laboratory Techniques: TFTs, which included Thyroxin (T4),free thyroxin (FT4) and thyroid stimulating hormone (TSH), were measured at the 1st visit, and on these quentially follow-up visits. FT4, TSH were measured by radioimmunoassay. Thyroglobulin and thyroid peroxidase antibodies were measured by agglutination test.

Statistical analysis: The data were entered into an the SPSS program, version 22.0 (IBM Corp. Released 2018. IBM SPSS Statistics for Windows, Version 22.0. NY, USA). Analysis correlation coefficient, Chi-Square test of independence used *p = 0.05 for the probability* level 0.05.

Operational definitions

Congenital Hypothyroidism(CH): Any patient with a high demonstrated within the newborn period (4-28 days of life).[5]

Subclinical hypothyroidism (SCH): Mildly elevated TSH (typically 5–10 mU/L) and normal total or free T4 level.[5]

Aquired Hypothyroidism(OHT): A high TSH level and corresponding low FT4 level after birth.

Hyperthyroidism: A low TSH and a high FT4 level.[5]

Children with normal thyroid hormone levels and TSH < 5 mU/L were followed up annually. In those with TSH levels between (6 -10 mU/mL), and FT4 in normal range, TFTs were repeated after 3 months. Patients with TSH >11 mU/L in the 1st year of their life were also retested after 2 weeks in order to exclude transient neonatal hypothyroidism or laboratory errors.

RESULTS

183 DS children were included in this study, aged between [5 days – 16 years], there was a slight female predominance (55%) [Figure 1]. Of the total of 183 DS children, TFTs were normal in 107 children (58%), and were found to be abnormal in 76 (42%) [Figure 2].

23 patients (30%) all of whom were diagnosed to have overt thyroid diseases. Overt thyroid diseases including,19 case (83%) with overt hypothyroidism, 1

case (4%) with CH, and 3 case (13%)with hyperthyroidism, while subclinical hypothyroidism (SH) was found in 53 patients (70%) [Table 1] & [figure2].
CH was found in one patient in this study, reflecting a frequency of (1%), A99mTc thyroid scan performed for him, showed normal position, shape and size of the thyroid gland.

19 patients (83%) had acquired hypothyroidism with positive thyroglobulin and thyroid peroxidase antibodies. All patients treated with thyroxin and have good response to the medical therapy.

3 patients(13%) had hyperthyroidism, they presented with weight loss or failure to gain weight, and tachycardia. Exophthalmos found in 2 patients, while goiter found in one patient only. All patients with hyperthyroidism were diagnosed to have Graves' disease and treated with methimazol with good response to the medical therapy in 2 cases, while one patient had frequent relapses, and at the age of 14 years, she treated with radioactive iodine, 8 months after; she developed overt hypothyroidism and managed with thyroxin therapy.

53 cases (70%) found to have SCH, which is the most common form of thyroid dysfunction in this study ,the mean TSH level of the cases was 8.9mU/L ranging [7.7-11.8 mU/L], those children were followed up regularly at pediatric endocrine clinic with the median follow up time of 6 and 12 months, respectively.

Out of 53 children with SCH, 35 patients (66%) showed a spontaneous decrease of TSH to normal level, mean TSH 1.1 mU/L ranged [0.5- 5.9], 10 patients (19%) showed persistently elevated TSH level, mean TSH level 17 ranged [13-32 mU/L], thyroxin therapy started for those children, while 8 case (15%) showed fluctuation in TSH level.

Regarding other congenital anomalies in this study, of the 183 children with DS, 89 patients (49%) had congenital heart diseases, and the commonest lesion was atrioventricularseptal defect, followed by ventricular septal defect, patent ductusarteriosus, and tetralogy of Fallot respectively.

Congenital gastrointestinal anomalies were found in 21 patients (11%), 5 cases with duodenal atresia, 8 cases with imperforated anus, Hirschprung disease noted in 5 cases, and 3 cases with malrotation.

Out of 183, there were 12 patients (7%) diagnosed to have celiac disease, and doing well on gluten free diet. There were 7 patients (4%) with hematological diseases: 4 cases with acute myeloblastic leukemia, and 3 cases with acute lymphoblastic leukemia, 9 cases in the study have type 1 diabetes. [Figure 3].

3 cases out of 9 had SCH, one case progress to an overt hypothyroidsm, and treated with levo-thyroxine therapy.

Concerning maternal age at childbirth was obtained in 175 children with DS. The mean maternal age was 33 years, ranged [19 - 47]. The maternal age of more than 35 years accounted for 64% of DS children.

Regarding family history in this study, we have 8 patients out of 76 children with DS had positive family history of thyroid disease, and almost all (7 out of 8) of them have thyroid disorders either over hypothyroidism or SCH.

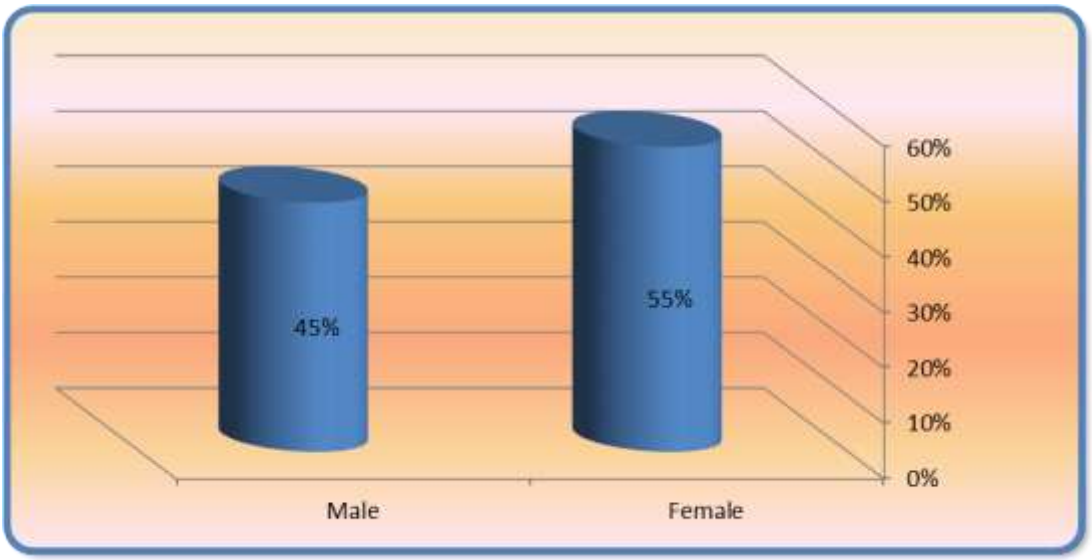


Figure 1: Sex wise distribution of studied down syndrome.

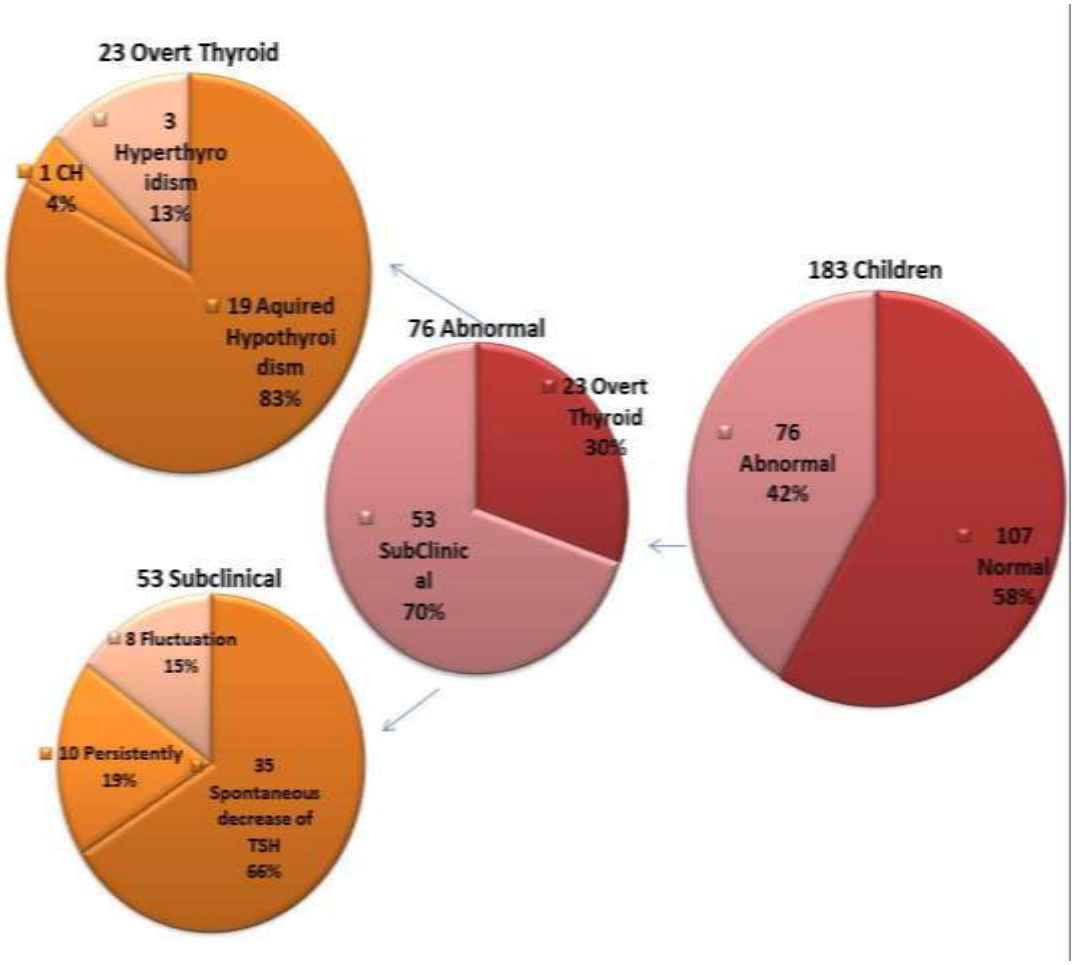
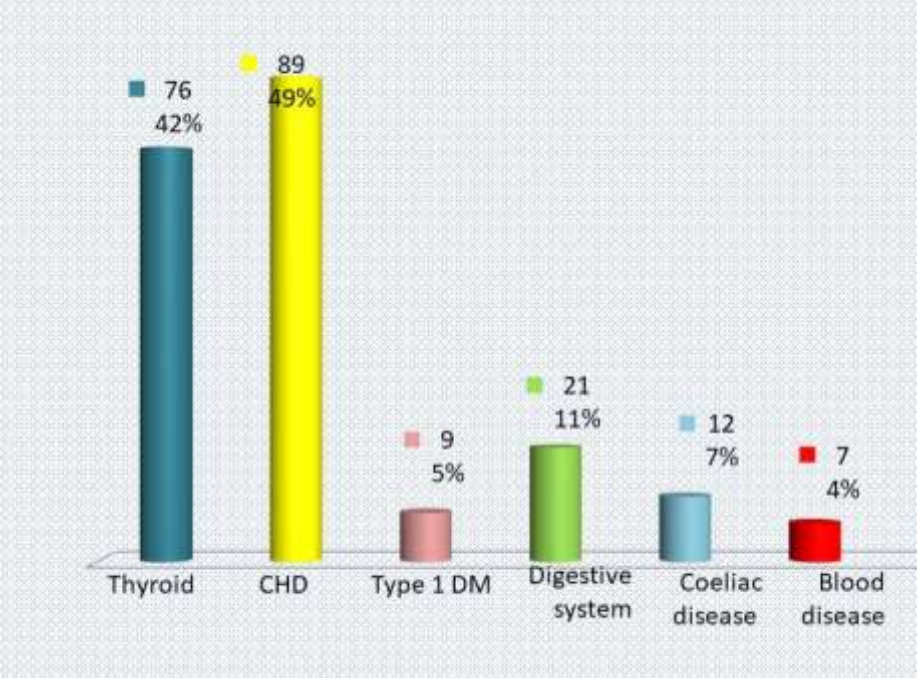


Figure 2: Distribution of the studied down syndrome according to thyroid abnormality.

Table 1: Distribution of the studied down syndrome according to thyroid abnormality.

Variable	Number	%
I DS with normal TFT	107	58
II DS with abnormal TFT :	76	42
1) Overt thyroid disease:	23	30
a - congenital hypothyroid	1	4
b- Acquired hypothyroid	19	83
c - Hyperthyroid	3	13
2) Subclinical :	53	70
a - Spontaneous TSH decrease	35	66
b - Persistent elevate TSH	10	19
c- Fluctuation in TSH	8	15



	Heart Disease	diabetes	digestive	Celiac	Blood Disease	FH	Maternal Age
thyroid	-.045-	-.038-	-.095-	-.044-	-.110-	.254**	-.077-

Figure 3: Distribution of associated diseases in the studied down syndrome patients.

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).
-Chi square among Thyroid and CHD=0.376 N.S
-Chi square among Thyroid and Diabetes = 0.262N. S
-Chi square among Thyroid and Digestive = 1.665N.S
-Chi square among Thyroid and Maternal age = 1.084 N.S
-Chi square among Thyroid and Celiac = 0.355 N.S.
-Chi square among Thyroid and Blood = 2.225 N.S.
-Chi square among Thyroid and FH = 11.778*** with significant at level 0.001.

DISCUSSION

Thyroid disease is a common co-morbidity in individuals with DS, patients with DS exhibit a wide range of thyroid dysfunction, especially hypothyroidism.

In our study, we have found that, the prevalence of thyroid dysfunction in children with DS was 42% (76 out of 183 cases).53 cases (70%) were SCH and 19 cases (83%) were acquired hypothyroidism. SCH represented more than two third of thyroid disorders in this study. In 35 cases out of 53, TSH level showed spontaneous decrease to the normal level within average of 6 to 12 months. 10 patients showed persistently elevated TSH level, and thyroxin therapy was started for them, while 8 case showed fluctuation in TSH level. In this study we have noted that the, prevalence of SCH is much higher than that reported to several studies,[5,10,21,22] which reported 6-44%.

The natural course of SCH in DS is variable, it may show a spontaneous decrease to normal or fluctuating serum TSH levels or developed overt hypothyroidism on follow-up.[10,22,23,24] The pathophysiology of SCH is not well understood, may be as a result of inappropriate TSH secretion related to hypothalamic pituitary dysfunction, or thyroid resistance to the level of TSH receptor, or a sign of evolving definite hypothyroidism. The clinical significance of SCH in DS children is also variable; some studies showed no significant difference on growth and development between these children to those with normal thyroid functions,[7,22] while Sharav et al found growth retardation in children with DS and SCH who were younger than 4 years,[22] and Karlsson et al found acceleration of growth after thyroxine treatment.[7] The therapeutic management remains a debatable issue: some endocrinologists recommend retesting in 3-6 months later, while others suggests treatment. In those identified with SCH, the authors suggest follow up and retesting more frequently.

Congenital hypothyroidism reported (1.3% or 1 in 76) in our study, which was comparable to the study of Fort[25] and Tüysüz.[11] Fort et al reported CH in 12 out of 1130 DS patients (1.1% or 1 in 94), which was 28 times greater than normal population.[25] Cutler et al reported a

prevalence of 6% (3 out of 49),[22] while Tüysüz reported a prevalence of 1.8% (6 out of 320).[11] The etiology for CH in DS patients is still unclear but does not appear to be due to autoimmune diseases since antibodies were not detected in these patients.[25,26] Unfortunately we consider the results regarding CH in this study unreliable, because till the time of writing this paper, the newborn screening program is not established yet in Libya.

In this study, we have noted that, the frequency of hyperthyroidism was 4% (3 cases out of 76), which is higher than the reports of several studies, which ranged from (0.87-2.5 %).[7,27,28] Hyperthyroidism occurs much less frequently than hypothyroidism in DS patients. It may be under diagnosed, due to a general lack of typical clinical features or a lack of awareness among physicians.

In this study we have noted that, there were no significant correlation between thyroid disorders in children with DS and the presence of either congenital heart diseases or congenital gastrointestinal anomalies, in other words; no significant difference was seen in the rate of thyroid disorders in DS children with congenital heart diseases or congenital gastrointestinal anomalies and those without congenital anomalies.

We also noted in this study that; there were no significant nearly no correlation between maternal age and thyroid disorders, rate of thyroid disorders in children with DS was the same either the children born to young or old mothers.

Regarding the family history of thyroid disorder in this study, 8 children out of 76 children with DS, had positive family history of thyroid disorders, and we have found a highly significant positive correlation between family history of thyroid disorders and thyroid disorders in DS children, almost all children (7 out of 8) with family history of thyroid disorder have thyroid dysfunction.

CONCLUSION

- Thyroid dysfunction is common among Libyan children with DS.
- Individuals with DS exhibit a wide range of thyroid dysfunction, especially hypothyroidism.
- SCH presented more than two-third of the thyroid dysfunction in this study.
- CH reported (1%) in this study.
- Frequency of hyperthyroidism in the study was 4%, which is higher than the reports of several studies.
- No significant correlation have seen in this study between thyroid dysfunction in children with DS and the presence of congenital anomalies as well as no significant nearly no correlation between thyroid dysfunction in DS children and maternal age, in contrast; we have observed a highly significant positive correlation between thyroid dysfunction in DS children and positive family history of thyroid dysfunction.

Recommendation

- Unfortunately; the newborn screening program is not established yet in Libya, we strongly recommend thyroid function screening program for newborn.
- we shouldn't ignore the subclinical cases during follow up for all suspected cases and close follow up are needed and retest TSH and FT4 in those who presented with SCH within 3-6 months before a decision is made to treat what could be a transient biochemical finding.

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