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Clinical Pattern of Acquired Thyroid Disorders in Childhood and Adolescents Attending Endocrine Unit, Tripoli Children Hospital

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Authors' contributions

This work was carried out in collaboration between all authors. Author FBR designed the study, wrote the protocol and first draft of the manuscript. Authors SG and GB performed the statistical analysis, managed the analyses of the study. All authors managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background and Aims: Thyroid disorders are one of the endocrine disorders commonly encountered in childhood and adolescence and they manifest with alternations in thyroid hormone secretions, goitre or both. Normal thyroid gland function is critical for early neurocognitive development, as well as for growth and development throughout childhood and adolescence.
This study was aimed to describe the clinical pattern of acquired thyroid disorders in children and adolescents.
Study Design: A descriptive cross-sectional hospital based study.
Place and Duration of Study: The study was conducted at the Tripoli Children hospital from January 2000 to December 2012.
Methodology: All Patients aged between 1- 18 with thyroid disorders, attending the pediatric endocrine clinic were included, the diagnosis of thyroid disorders was based on clinical features,

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thyroid function tests and anti-thyroid antibodies test. Data included age, gender, clinical features, duration of symptoms before diagnosis, results of investigations including blood tests, bone age x-ray and result of brain Magnetic Resonance Imaging (MRI), family history of autoimmune disease and any associated problem. Data were analysed using the SPSS program.

Results: During 12 years period under review, 148 patients (5.9%) had thyroid disorders, 135 (91.22%) patients had hypothyroidism, 11(7.43%) had hyperthyroidism, 2 (1.35%) had a goitre in euthyroid state. Mean age at presentation for primary hypothyroid was 9 ± 3.8 years, for secondary hypothyroidism was 7 ± 1.5 years, for hyperthyroid was 9.8± 2.2 years and for euthyroid goitre was 9.2± 2.1 years. Male to female ratio was 1:1.3**.** The family history of autoimmune disease was positive in 33 patients (22.3%), in 29 (41.43%) patients of primary hypothyroidism and 4 (100%) patients with Graves' disease were had a positive family history. Mean duration of symptoms before presentation was 0.43± 0.1 years for primary hypothyroidism and 1.4±0.21 years for secondary hypothyroidism while for patients with hyperthyroidism was 0.7±0.15 years, in two children with euthyroid goitre was 0.8 years. About 31% of patients with hypothyroidism were of short stature followed by fatigability and sleepiness (23.9%). About 64% of patients with hyperthyroidism had goitre and eye signs followed by palpitation and weight loss (54.5%). There were co morbidities in 75 children out of 148 patients as a result of growth hormone deficiency, diabetes mellitus and some other syndromes. Anti-thyroglobulin antibodies were positive in 21(14.2%) patients, Thyro-peroxidase antibodies were positive in 26 (17.6%) patients**.** Bone age estimation was delayed in 73(49.3%), advanced in 7(4.7%) patients. Brain MRI was done for 46 patients; which showed pituitary hypoplasia in 15.5%, 10.8% had normal brain MRI, in 4.7% of patients MRI showed other findings.

Conclusion: hypothyroidism constituted the greatest proportion of the thyroid disorders in children and short stature is the commonest presenting symptoms of a hypothyroid child, paediatricians should be aware of the need to screen children who present with a short stature for hypothyroidism.

Keywords: Thyroid disorders; hypothyroidism; short stature; thyroid function test; children.

1. INTRODUCTION

Thyroid disorders are one of the endocrine disorders commonly encountered in childhood and adolescence and they manifest with alternations in thyroid hormone secretions, goitre or both. Insufficient hormone secretion results in hypothyroidism and excessive secretion causes hyperthyroidism, sometimes goitre exists with normal thyroid function. Normal thyroid gland function is critical for early neurocognitive development, as well as for growth and development throughout childhood and adolescence [1]. Hypothyroidism is the most common disturbance of thyroid function in children, acquired hypothyroidism can be either primary (thyroid disease) or secondary to a central cause (hypothalamic-pituitary disease), autoimmune destruction, iodine deficiency and infiltrative disease could lead to primary thyroid gland failure, iatrogenic forms of hypothyroidism occur after thyroid surgery or radioiodine therapy [2]. Autoimmune hypothyroidism is the most common cause of acquired hypothyroidism in children, adolescents and adults; the prevalence of autoimmune hypothyroidism in childhood is an estimated 1% to 2% with 4:1 female predominance, approximately 50% of cases have a family history of autoimmune thyroid disease [3]. Several syndromes are associated with an increased risk for developing autoimmune hypothyroidism, including Down syndrome and Turner syndrome [4,5]. An additional autoimmune disorder in the same patient is also associated with an increased risk of diabetes, alopecia, vitiligo and celiac disease [6]. The most common clinical presentation of hypothyroidism are fatigue, cold intolerance, constipation, poor linear growth and if undiagnosed may compromise adult height [3]. Hyperthyroidism accounts for 15% of pediatric thyroid disorders, with most cases attributable to autoimmune hyperthyroidism known by Graves' disease. The incidence of Graves' disease among pediatric patients is 0.1 to 3 cases per 100,000 children [7], Graves' disease is more prevalent among females, with a peak incidence between 10 and 15 years of age [8] and associated with other autoimmune diseases with the family or in the same patient as well as other syndromes such as Down and Turner syndromes [9], however less common etiologies of hyperthyroidism, including infections or drug-induced [8]. It's pathogenesis attributed to either the destruction of the thyroid follicles causing the release of supra physiologic level of T3 and T4 resulting in thyrotoxicosis or

the inappropriate production of thyroid hormones from the nondestructive process including Graves' disease or toxic multinodular goitre [10]. The most presentations include restlessness or fidgetiness, warm moist skin, proximal muscle weakness and an enlarged thyroid gland (goitre). Graves's ophthalmopathy occurs in up one-third of pediatric patients, however, in contrast to adults, it is typically mild and most frequently improves if the child with Graves' disease achieves remission [11]. Children and adolescents may also present with alternations in growth, including growth acceleration and advanced bone age [11].

The study was aimed to describe the clinical pattern of acquired thyroid disorders in children and adolescents.

2. PATIENTS AND METHODS

- **Study design:** A descriptive cross-sectional hospital-based study.
- **Study setting:** Study was conducted at the Endocrine clinic, Tripoli Children hospital, Tripoli-Libya.
- **Period of study:** 10 years by reviewing all patient's records from January 2000 to December 2012.
- **Study population:** All endocrine patients' records (2500) who were seen at the endocrine clinic during the period of study.
- **Inclusion criteria**: All patients aged between 1- 18 with acquired thyroid disorders.
- **Exclusion criteria**: Patients with congenital thyroid disorders.
- **Sample size**: 148 patients.
- **Diagnostic tool**: Diagnosis of thyroid disorders was based on clinical features and thyroid function tests which included determination of TSH, free thyroxin level and free triiodothyronine and anti-thyroid antibodies. Secondary hypothyroidism was defined as low thyroxine level with low or inappropriately normal thyroid stimulating hormone.

Analyses were performed by electrochemiluminescence immunoassay using the Cobas 6000 (Roche Diagnostics) module e601. The methodology for TSH analysis is a two-point sandwich assay while the FT4 assay is a competitive indirect test. Study considered the following normal values for TSH, FT4 and FT3 according to different age groups: TSH: ***1***-5 years (0.7-6.0 mIU/L), 6-10 years (0.6-4.8 mIU/L) and 11-19 years (0.5-4.3 mIU/L) [12]. FT4:1-5 years (1.0-1.8 ng/dL), 6-19 years (1.0-1.7 ng/dL). [12] FT3 > or =1 year (2.8-4.4 pg/mL) [13].

- **Study tool:** Data collected by using case sheet including age, gender, clinical features, duration of symptoms before diagnosis, results of investigations including blood tests, bone age x-ray and result of MRI brain, family history of autoimmune disease and any associated diseases.
- **Data analysis:** Data were organised and analysed using the SPSS program version 16. Descriptive statistics including means, standard deviation, frequencies, and percentages were done for all variables as appropriate.

3. RESULTS

During 12 years period under review, a total of 2500 new cases were seen at the pediatric endocrine clinic, out of these number 148 (5.9%) had thyroid disorders, out of which 135 (91.22%) children had hypothyroidism, 11(7.43%) had hyperthyroidism and 2 (1.35%) were had euthyroid goitre. There were 70 (47.3%) patients with primary hypothyroidism and 65(43.9%) with secondary hypothyroidism, 7(4.7%) patients had thyrotoxicosis and 4 (2.7%) with Graves ' disease. (Fig. 1).

3.1 Demographic Characteristic of Patients

The study showed that mean age at presentation for hypothyroid patients with the primary cause was 9 $\pm$ 3.8 years, for patients with secondary hypothyroidism was 7 $\pm$ 1.5 years, hyperthyroid was 9.8$\pm$ 2.2 years and for euthyroid goitre was 9.2$\pm$ 2.1 years.

The study revealed that overall male to female ratio was 1:1.3 (Fig. 2).

Concerning the family history of autoimmune disease, the study showed that 33 (22.3%) patients with thyroid disorder had a positive family history. Twenty-nine (41.4%) of primary hypothyroidism and all patients with Graves' disease had a positive family history.

Mean duration of symptoms before presentation was 0.43$\pm$ 0.1 years for primary hypothyroidism

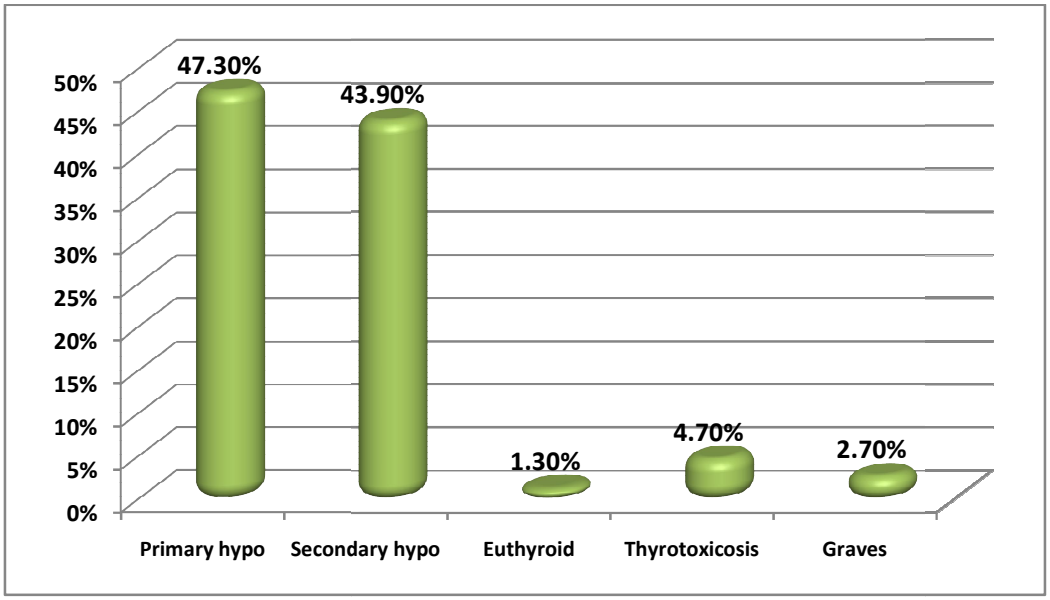

Fig. 1. Distribution of patients followed at endocrine clinic in Tripoli Children Hospital by type of thyroid disorder

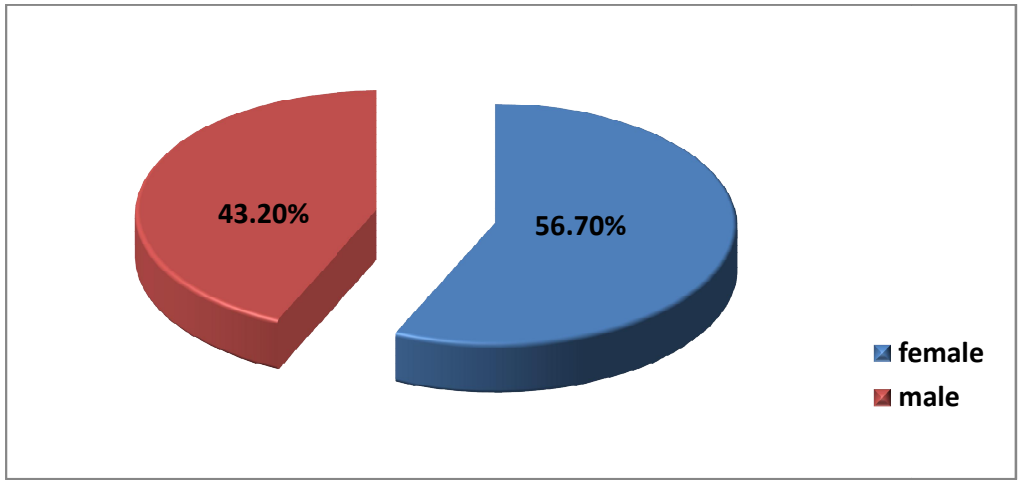

Fig. 2. Gender distribution of patients with thyroid disorders

and 1.4±0.21 years for secondary hypothyroidism; while for patients with hyperthyroidism it was 0.7±0.15 years, the presence of symptoms before presentation in two children with euthyroid state was 0.8 years.

Regarding the clinical presentation of patients with hypothyroidism, Fig. 3 showed that (31.2%) of children were of short stature followed by fatigability and sleepiness (23.9%).

Patients with hyperthyroidism who had a goiter and eye signs were 63.6%, followed by palpitation and weight loss (54.5%) and other clinical features (Fig. 4).

Comorbidities were identified in 75 (50.7%) children, the commonest being growth hormone deficiency, Down syndrome followed by T1 DM and others (Fig. 5).

Diagnosis of thyroid disorders was based on laboratory finding including TSH, FT3, FT4; the diagnosis of autoimmune thyroiditis based on Antithyroid antibody testing. Thyro-peroxidase antibodies were positive in 26(17.6%) patients,

Anti-thyroglobulin antibody was positive in 21(14.2%) patients. Regarding bone age estimation, it was delayed in 73(49.3%), advanced in 7(4.7%), normal in 31(21%), and it was not done for 37 patients. Brain magnetic resonance imaging was done for 46 patients, 15.5% MRI showed pituitary hypoplasia, 10.8% had normal findings, in 4.7% of patients MRI showed other findings (Table 1).

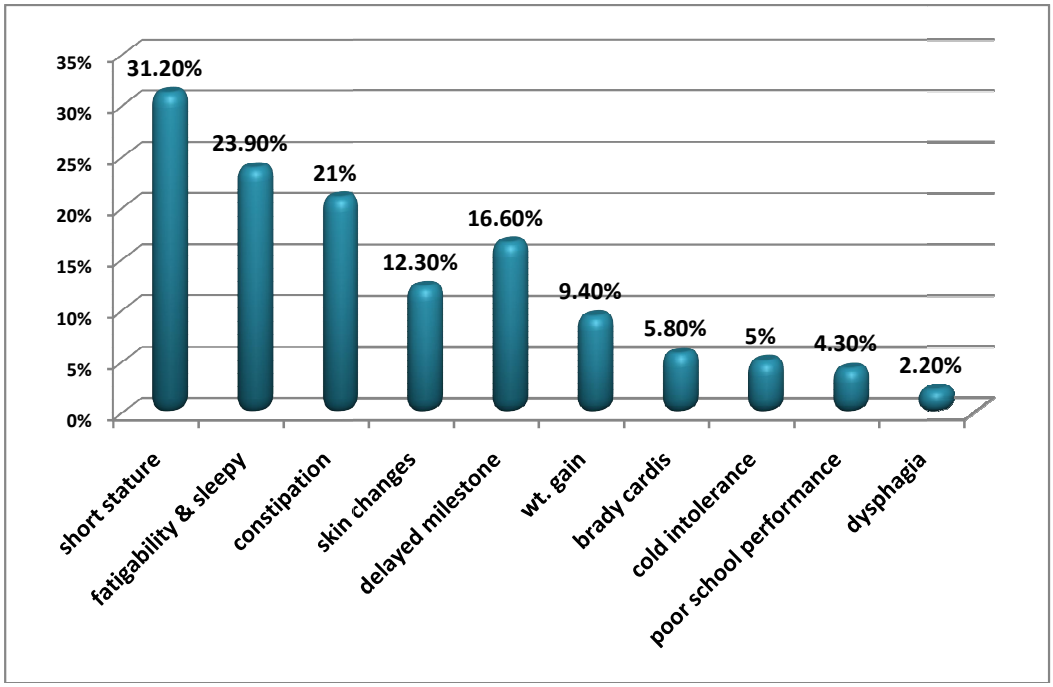

Fig. 3. Distribution of patients with hypothyroidism by clinical presentation

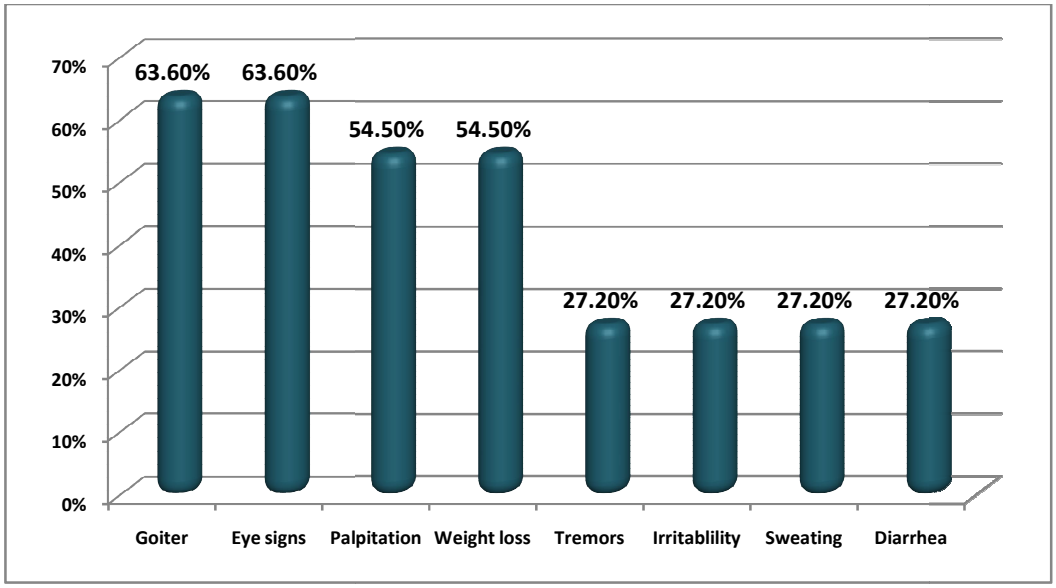

Fig. 4. Distributions of hyperthyroid patients by the common clinical presentation

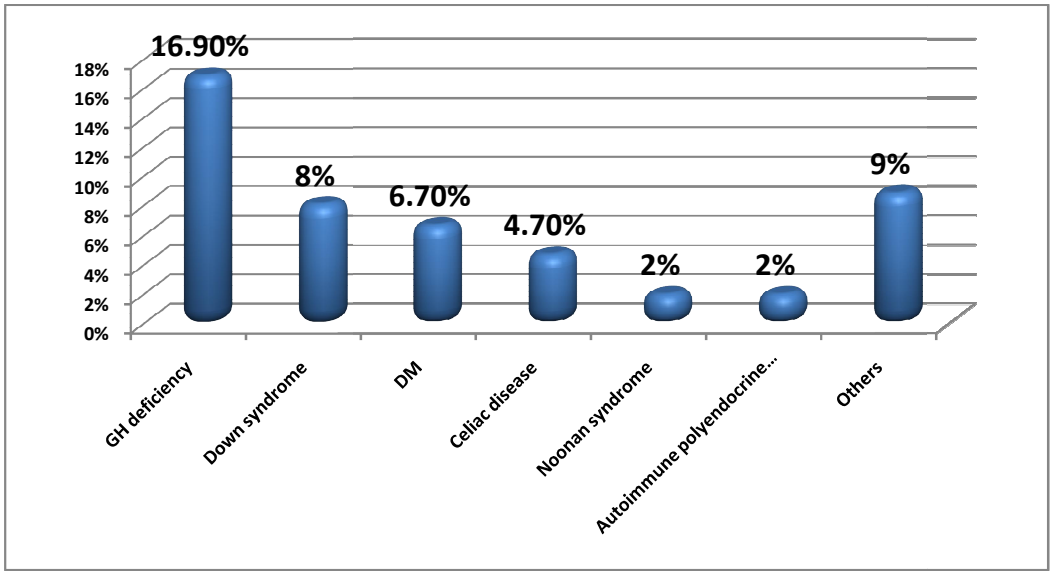

Fig. 5. Distribution of patients under study according to comorbidity

Table 1. Results of diagnostic parameters of thyroid disorder in patients under study

Investigation	Frequency	Percentage
Positive antithyroid antibodies		
Thyro Peroxidase antibodies	26	17.6
Thyroglobulin antibodies	21	14.2
Not done	101	68.2
Bone age		
Delayed	73	49.3
Advanced	7	4.7
Normal	31	21
Not done	37	25
Brain MRI finding		
Pituitary hypoplasia	23	15.5
Normal	16	10.8
Other findings	7	4.7
Not done	102	69

4. DISCUSSION

Thyroid disorders in the children and adolescents are common, the number had increased dramatically in the past years, and there is no real explanation for that. Acquired hypothyroidism is the most common abnormality of thyroid function in children and most often caused by autoimmune thyroiditis [14]. In this study hypothyroidism is the commonest disorder going with Yellurisk study 30.6% of studied patients were hypothyroid and 11.1% were hyperthyroid, the most common cause was found to be acquired hypothyroidism (47.2%) [15], also Amitabh Singh et al. [16], showed 93.8% of patients had hypothyroidism and 6.1% had hyperthyroidism, Onyiriuka showed disagreement with present results, which revealed 66.7% of studied patients had hyperthyroidism and 22.2% had hypothyroidism [17].

Male to female ratio is 1:1.3, which is not surprising as most studies reported a female predominance [14,15,17].

The reasons for the sex difference are unknown. The mean age at diagnosis for hypothyroid patients is 9±3. 8 years. A study of acquired thyroid disorders conducted in Saudi Arabia showed the mean age at diagnosis was 8 years for acquired hypothyroidism [14], Onyiriuka revealed that the majority of the patients with thyroid disorder presented during adolescence with the mean age of 11.2 years [17], most of

their patients are hyperthyroid, which is in accordance with the present study, the mean age of diagnosis of patient is 8-9 years. Current study revealed about a quarter of the patients had positive family history of auto immune disease, 41.4 % of patients with primary hypothyroidism and all patients with Graves' disease; a study conducted in 2016 by Amitabh et al. [16] reported only 6.5 % of cases with hypothyroid had family history of auto immune disease, but none of the hyperthyroid children had positive family history, while another study conducted in Nigeria by Onyiriuka et al. [17] found no positive family history of thyroid disorders in any of the patients.

The duration of symptoms before presentation was shorter in primary hypothyroidism and hyperthyroidism than secondary hypothyroidism patients. These finding may be explained by that most of autoimmune hypothyroidism patients were associated with diabetes, celiac, Down syndrome and are usually diagnosed by an annual screening; also presence of goitre might have contributed to the shorter duration of symptoms before presentation. Onyiriuka et al. [17] showed that duration of symptoms before presentation was shorter in hyperthyroidism, this was explained by the more insidious onset of hypothyroidism and presence of goitre in hyperthyroidism. Short stature is a well-recognised consequence of hypothyroidism during childhood and can be one of the presenting symptoms. In the current study more than a quarter of hypothyroid patients had short stature. The same result was concluded by Al-Agha and AL shugair in Saudi Arabia [14], showing 33.5% of patients with hypothyroidism presented with short stature. An Indian study reported a prevalence of short stature (45%) among juvenile hypothyroid patients with height SDS - 2.9 ± 0.9, Amitabh et al. [16], showed the commonest clinical presentation in patients with hypothyroidism was short stature (59%) hence, paediatricians should be aware of the need to screen children who are presented with short stature for hypothyroidism. Regarding hyperthyroid patients in the current study, more than half of them presented with goitre and eye signs. In Amitabh et al. [16] study 100% of hyperthyroid patients had tachycardia and goitre was present in 50% of patients.

There were comorbidities observed in most the patients with thyroid dysfunction, like some chromosomal disorders as Down syndrome, Turner or other auto immune disorders such as Type1DM and celiac disease. In Down syndrome there's an increased risk of developing autoimmune thyroid disease which also has been demonstrated by many studies as Mak et al. [18], Larsson [19], and study conducted in Kuwait by Ali et al. [20] on Down syndrome.

A study conducted in Saudi Arabia in 2016 showed that 8% of patients with acquired hypothyroidism had Down syndrome [14]. Some studies recommend annual screening for thyroid function in patients with Down syndrome because the symptoms of hypothyroidism might be mistaken for symptoms related to the natural course of Down syndrome [21]. A study on Chinese girls with Turner syndrome showed that hypothyroidism is common especially in those older than 5 years and routine thyroid testing is advocated thereafter on a yearly basis [22]. Patients with TIDM, have a higher prevalence of thyroid disorders than the normal population, 30% of patients with T1DM develop autoimmune thyroiditis and as much as 20–30% of the population with T1DM express thyro-peroxidase antibodies and/or thyroglobulin autoantibodies [23]. The association between T1DM and autoimmune thyroid diseases has long been recognised. In the current study 10 patients had T1DM (6.7%), more ever, a study conducted in Turkey by Şimsek [24] on autoimmune thyroid diseases in children with T1DM that included 1032 patients, showed that 12% of patients had chronic lymphocytic thyroiditis, seven patients were celiac. In the present study 8.9% of auto immune thyroid patients were celiac, which is higher in compare with Sari [25] where 4.9% of patients with auto immune thyroiditis had celiac.

The most appropriate tests required to diagnose a child with thyroid disorders are serum TSH and thyroid hormones freeT3 and freeT4. It is useful to establish the presence or absence of thyroid antibodies but we could not do this for all patients because of suboptimal diagnostic facility. Bone age estimation was not performed in all the cases, about half of patients had delayed bone age. Amitabh et al. [16] showed 29.3% of patients with hypothyroidism had delayed bone age, while the children with hyperthyroidism had normal bone age.

5. CONCLUSION

Hypothyroidism constituted the greatest proportion of the thyroid disorders in children and adolescents. Short stature is the commonest presenting symptoms of the hypothyroid child.

6. RECOMMENDATION

Paediatricians should be aware of screen children who have a short stature for hypothyroidism. Screen patients with T1DM, celiac disease and certain syndromes (Down &Turner) for thyroid disorder. Further studies are needed in large scale and more diagnostic procedures as Ultrasonography of Thyroid gland should be used.

CONSENT

All authors declare that verbal informed consent was obtained from all participants during their follow up at the clinic and data confidentiality was maintained throughout the study and any resulting publication anonymously.

ETHICAL APPROVAL

The study was approved ethically by Tripoli Children Hospital committee for scientific research and permission also obtained from the research and consulting department at the faculty of the medicine-University of Tripoli for publication.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Desai MP. Disorders of thyroid gland in IAP textbook of pediatrics, 4th edition. NEW Delhi, Jaypee Brothers medical publishers Ltd, 2009;931-935.
2. Hanley P, Lord K, Bauer J, Thyroid Disorders in Children and Adolescents. A Review JAMA Pediatr. 2016;170(10): 1008-1019.
   DOI: 10.1001/jamapediatrics.2016.0486
3. de Vreis L, Bulvik. chronic autoimmune thyroidities in children and adolescents. Arch Dis child. 2009;94(1):33-37.
   DOI: 10.1136/adc.2007.134841
4. Gibson P, Newton R, Selby K, Price D, Leyland K, Addison G. longitudinal study of thyroid function in Down syndrome. Arch Dis Child. 2005; 90(6):574-578.
   DOI: 10.1136/adc.2004.049536
   (Accessed: 16 May 2018)
   Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1720431/
5. Yeşilkaya E, Bereket A, Darendeliler F, Bas F, Poyrazoglu S, Aydin B, et al. Turner syndrome and associated problems in Turkish children: A multicenter study. J Clin Res Pediatr Endocrinol. 2015;7(1):27-36.
   DOI: 10.4274/jcrpe.1771
   Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4439889/
   (Accessed 25 March 2018)
6. Karavanaki K, Kakleas K, Paschali E, Kefalas N, Konstantopoulos I, Petrou V et al. Screening for associated autoimmunity in children and adolescents with type 1 diabetes mellitus (T1DM). Horm Res. 2009;71(4):201-206.
   DOI: 10.1159/000201108
7. Lavard L, Ranløv I, Perrild H, Andersen O, Jacobsen BB. Incidence of juvenile thyrotoxicosis in Denmark. Eur J Endocrinol. 1994;130(6):565-568.
8. Wiliamson S, Greene SA, incidence of thyrotoxicosis in childhood, a national population based study in the UK and Ireland. Clin Endocrinol 2010;72:358-363.
   DOI: 10.1111/j.1365-2265.2009.03717.x
   (Accessed 10 May 2018)
   Available:https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1365-2265.2009.03717.x
9. Hemminki K The epidemiology of Graves' disease, evidence of a genetic and an environmental contribution. J Autoimmun. 2010; 34(3):J307-13.
   DOI: 10.1016/j.jaut.2009.11.019
10. Singh I, Hershman JM. Pathogenesis of hyperthyroidism. compr physiol. 2016; 7(1):67-79.
    DOI: 10.1002/cphy.c160001
11. Goldstein SM. Pediatric thyroid associated orbitopathy, the childrens hospital of philadelphia experience and Literature review of thyroid. 2008;18(9):997-999.
    DOI: 10.1089/thy.2008.0014
12. Melmed S, Polonsky KS, Larsen PR, et al. Williams textbook of endocrinology. 12th edition, Elsevier Saunders Company. 2011;348-414.
13. Demers LM, Spencer Cl. The thyroid: pathophysiology and thyroid function testing. In: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. Fourth edition. Edited by CA Burtis, ER Ashwood, DE Bruns. St. Louis, Elsevier Saunders Company. 2006;2053-2087.
14. Al Agha AE, AL shugair RM. Clinical presentation of acquired hypothyroidism

and associated disorders in children and adolescents at King Abdul Aziz university hospital in a western region of Saudi Arabia. J Pat Care. 2016;2:123.
DOI : 10.4172/2573-4598

15. Yelluri SK. Incidence and etiology of thyroid disorder in children. Int J Contemp Pediatr. 2016;3(2):593-596.
DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20161045
(Accessed 20 April 2018)
Available:https://www.ejmanager.com/mnstemps/119/119-1455163512.pdf
16. Singh A, Purani C, Mandal A, Mehariya KM, Das RR. Prevalence of thyroid disorders in children at a tertairy care hospital in western India. J Clin Diagn Res. 2016;10(2):SC01–SC04.
DOI: 10.7860/JCDR/2016/16315.7189
(Accessed 13 May 2018)
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4800610/
17. Onyiriuka AN, Abiodun PO, Onyiriuka LC. Thyroid disorder in children and adolescent in Nigerian teaching hospital. Greener Journal of Medical Sciences. 2012;2(2): 45-50.
(Accessed 15 May 2018)
Available:https://pdfs.semanticscholar.org/14e6/0ca924a87f0d5cc6a2e50f97bbb06a016157.pdf.
18. Mak P, But W, YU C, Chow C, Li K, Lee L et al. Thyroid dysfunction in Chinese children and adolescents with Down syndrome HK J paediatr. 2006;11:110-117.
(Accessed 16 May 2018)
Available:http://www.hkjpaed.org/pdf/2006;11:110-117.pdf
19. Ivarsson SA, Ericsson UB, et.al. The impact of thyroid autoimmunity in children and adolescents with Down syndrome.
Available:https://doi.org/10.1111/j.1651-2227.1997.tb14808.x
20. Ali FE, bayoumy HA, Mohammad AR, Al-Busairi WA, Al-Othman AA. Thyroid function in Kuwait subjects with Down syndrome. Med Principles Pract. 2002; 11:206–209.
DOI: 10.1159/000065807
(Accessed 16 April 2018)
Available:https://www.karger.com/Article/Pdf/65807
21. Karlsson B, Gustafsson J, Hedov G, Ivarsson SA, Annerén G. Thyroid dysfunction in Down's syndrome: Relation to age and thyroid autoimmunity. Arch Dis Child. 1998;79(3):242–245.
(Accessed 21 May 2018)
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1717691/pdf/v079p00242.pdf
22. Chen RM, Zhang, Yang XH, Lin XQ, Yuan. Thyroid disease in Chinese girls with turner syndrome. Journal of Pediatric Endocrinology & Metabolism: JPEM Jan 2015;28(1-2):201-205.
(Accessed 22 May 2018)
23. Baker JM. Clinical review type 1 diabetes associated auto immunity: Natural history, Genetic associations and Screening. J Clin Endocrinol Metab, l. 2006;91(4):1210–1217.
DOI: 10.1210/jc.2005-1679
(Accessed 22 May 2018)
Available:https://academic.oup.com/jcem/article-df/91/4/1210/10779173/jcem1210.pdf
24. Şimsek DG, Aycan Z, Özen S, Cetinkaya S, Kara C, Abalı S, et al. Diabetes care, glycemic control, complications, and concomitant autoimmune diseases in children with type 1 diabetes in Turkey: A Multicenter Study. Clin Res Pediatr Endocrinol 2013;5(1):20-26.
DOI: 10.4274/Jcrpe.893
(Accessed 21 May 2018)
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3628388/pdf/JCRPE-5-20.pdf
25. Sari S, Yesilkaya E, Egritas O, Bideci A, Dalgic B. Prevalence of celiac disease in Turkish children with autoimmune thyroiditis. Digestive Diseases and Sciences. 2009,54(4):830–832.
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