Original Article

Pattern of Thyroid Disorders in Children and Adolescents Seen at the Lagos University Teaching Hospital, Nigeria, Over a 10-year Period

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Abstract

Introduction: Thyroid disorders account for a large proportion of pediatric endocrine disorders. Untreated hypothyroidism in childhood has permanent adverse effects on physical, intellectual, and neurological development. However, few studies have reported the pattern of pediatric thyroid disorders in Nigeria. **Objectives:** The objective of this study was to document the pattern of thyroid disorders in children and adolescents seen at the Lagos University Teaching Hospital (LUTH) over a 10-year period. **Participants and Methods:** This is a retrospective descriptive study involving children with thyroid disorders seen from January 1, 2006 to December 31, 2015. **Results:** Seventy-one patients with thyroid disorders (0.13%) were seen out of 52,800 new cases (incidence of 1/1000 new cases) comprising 13.4% of 546 pediatric endocrine cases with a male:female ratio of 1:1.2. Median (range) age at presentation was 1.6 (0.001–14) years. Congenital hypothyroidism (CH) constituted a major proportion of cases (46.7%), with a median (range) age at presentation of 9 (1.5–24) months. Down syndrome constituted 45% of patients with CH with associated congenital heart defects in eight (53%) patients. Acquired hypothyroidism was seen in ten patients (five goitrous and five nongoitrous). Six patients had hypothyroidism associated with multiple anterior pituitary hormone deficiency. Nine patients (all females) had hyperthyroidism with confirmed Graves' disease in 5 (55.6%), with mean age at presentation being 9.4 ± 2.09 years. Other conditions were euthyroid sick syndrome (2.8%), euthyroid goiter (1.4%), and acute thyroiditis (1.4%). Eight infants of mothers on treatment for hyperthyroidism (first seen between the 7th h of life to 2 months of age) had transient hypothyroidism while one 8-day-old had transient hyperthyroidism. **Conclusion:** CH was the most common disorder encountered with late age at presentation. Routine newborn screening and maintaining a high index of suspicion are advocated.

Keywords: Children, Down syndrome, Graves' disease, hyperthyroidism, hypothyroidism, thyroid disorders

Introduction

Thyroid disorders account for a large proportion of pediatric endocrine disorders, being the second most common after diabetes in children worldwide.[1] Thyroid dysfunction in infancy and childhood results in metabolic abnormalities and also affects growth and development.[2] Thyroid hormone-dependent effects on tissue maturation are developmentally regulated and organ or tissue specific, hence the clinical consequences of thyroid dysfunction depend on the age of the infant or child.[2] Untreated hypothyroidism in the fetus or newborn infant results in permanent abnormalities in intellectual and/or neurological function, while after the age of 3 years, hypothyroidism results in slow growth and delayed skeletal maturation.[2] The UNICEF estimates state that 8% of newborns from sub-Saharan Africa are unprotected from learning disabilities resulting from iodine deficiency-related disorders.[3] In children and adolescents, the range of iodine deficiency disorders includes goiter, subclinical hypothyroidism, impaired mental function, retarded physical

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development, and increased susceptibility of the thyroid gland to nuclear radiation.[3]

In spite of the well-recognized profound effect of thyroid dysfunction in children, there are very few studies that have examined childhood and adolescent thyroid disorders in Nigeria.[4-7] The incidence of thyroid disorders in children appears to be increasing.[6] The etiology, prevalence, clinical presentation, and clinical course of thyroid disorders in children and adolescents substantially differ from that of adults.[8] Furthermore, studies have also shown that thyroid anomalies differ from one population to another.[6] Therefore, this study sought to document the pattern of thyroid disorders in children and adolescents seen at the Lagos University Teaching Hospital (LUTH) over a 10-year period and highlight some management challenges encountered. It is hoped that awareness can be created about the pediatric thyroid disorders in our environment to facilitate timely diagnosis and prompt management.

Participants and Methods

This was a retrospective descriptive study in which data were extracted from the case records of all the patients aged from birth to 18 years with thyroid disorders seen at the LUTH from January 1, 2006 to December 31, 2015. Sociodemographic information and other information such as age at presentation and presenting symptoms were extracted. Other relevant information such as duration of symptoms before presentation, examination findings at presentation, investigation results, complications, family history of thyroid disorders, and management were also extracted. Thyroid disorders were diagnosed based on clinical presentation, thyroid function tests (free thyroxine [FT4], free triiodothyronine [FT3], and serum thyroid-stimulating hormone [TSH]), serological tests, and radiological imaging.

The Health Research and Ethics Committee of the LUTH approved the study and waived the requirement for informed consent. Data extracted were collated on a Microsoft 2010 Excel sheet and analyzed with SPSS version 20 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp). Univariate analysis was carried out for all major variables of interest. Continuous variables were tested for skewness of distribution. Normally distributed variables were presented as mean (±standard deviation) while skewed data were summarized using median with minimum and maximum values (range). Where applicable, the World Health Organization (WHO, Geneva)[9] AnthroPlus software was used to refer anthropometric variables which had been converted to Z-scores and referenced to the WHO Child Growth Standards and WHO Reference 2007. Weight-for-age Z-scores (WAZ) could not be computed for children aged ≥10 years because the WHO Reference 2007 did not provide standards for this age group. Using this reference, children with height-for-age Z-score (HAZ) <−3, −3 to <−2, −2 to + 3, and >+3 were classified as severe stunting, stunting, normal, and very tall, respectively, while body-mass-index-for-age Z-score (BMIZ) <−3 is severe wasting, −3–<−2 is wasting, −2 to +2 is normal, >+2 to +3 is overweight, and >+3 is obese.[10]

Results

A total of 546 children with endocrine diseases were seen out of 52,800 new cases in the outpatient clinics (incidence of 1.03%). Seventy-one out of these children had thyroid disorders, thus constituting 0.13% of all cases (incidence of 1 per 1000 of new cases) and 13.4% of the pediatric endocrine diseases. There were 32 males and 39 females with a male: female ratio of 1:1.2. The median (range) age at presentation was 1.6 (0.001–14) years. The youngest patient was a 7-h-old newborn female infant that was born to a mother being managed for Graves' disease. Table 1 summarizes the different diagnoses seen in the patients.

Children with CH constituted the greatest majority of the patients (46.7%). Among these, 17 children (11 males, 9 females) were managed for CH without an obvious clinical syndrome with a male:female ratio of 1.2:1. Two out of these 17 cases (a 4-year-old male and a 19-month-old female) were privileged to be delivered in a country where newborn screening for CH was available and were diagnosed shortly after birth and subsequently commenced on thyroid hormone replacement with L-thyroxine. These two patients presented to our center for follow-up. The median (range) age at presentation of the remaining 15 was 9 (range: 1.5–24) months. The major presenting features were poor growth, delayed achievement of developmental milestones, and excessive sleepiness/sluggishness among others as shown in Figure 1. One of the female children with CH who presented at the age of 5 months was also subsequently diagnosed with sickle cell anemia at the age of 4 years.

Table 1: Different groups of diagnoses of the patients

Diagnosis	Number of patients	Percentage of total
CH		
Nonsyndromic (17)	33	46.5
Associated with DS (15)		
Associated with Noonan syndrome (1)		
AH		
Goitrous (5)	10	14.1
Nongoitrous (5)		
Hypothyroidism associated with MAPHD	6	8.5
Graves' disease	9	12.7
ESS	2	2.8
Simple goiter (euthyroid)	1	1.4
Acute thyroiditis	1	1.4
Infants of hyperthyroid mothers		
Transient hypothyroidism (8)	9	12.7
Transient hyperthyroidism (1)		
Total	71	100.0

CH – Congenital hypothyroidism; DS – Down syndrome; AH – Acquired hypothyroidism; MAPHD – Multiple anterior pituitary hormone deficiency; ESS – Euthyroid sick syndrome

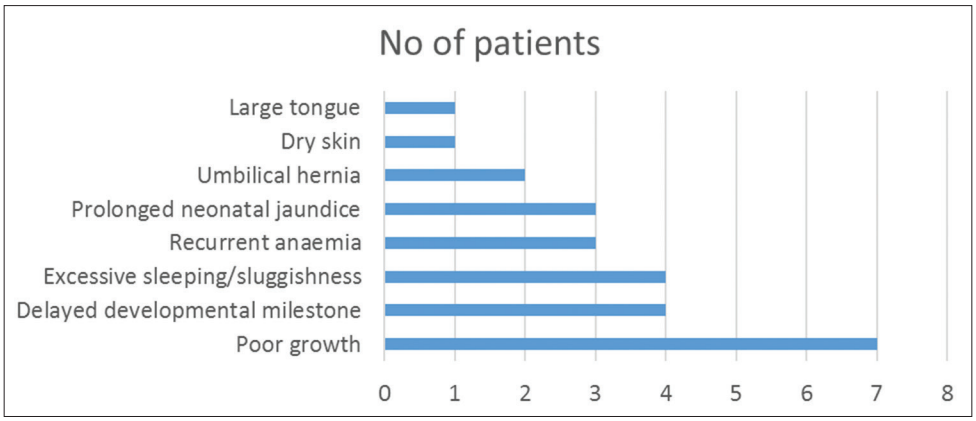

Figure 1: Presenting clinical features in patients with congenital hypothyroidism

The next major group of children being managed for CH included patients with Down syndrome (DS). They comprised of nine males and six females giving a male: female ratio of 1.5:1 and constituted 45% of the total patients managed for CH. The median (range) age at presentation of these patients was 9 (range: 3–60) months. Eight (53%) out of the 15 cases of DS had associated congenital heart defects. One patient also presented at 18 days of age with features of Noonan syndrome and associated CH.

The patients managed for acquired hypothyroidism (AH) comprised of six males and four females (male:female ratio of 1.5:1). The median (range) age at presentation was 6.75 (range: 3–13) years. Associated conditions in the five patients with nongoitrous cases included obesity, seizure disorder, precocious puberty, tuberculosis, and a combination of autoimmune thyroiditis with vitiligo, respectively. Among the other five who had a goiter at presentation, antithyroid peroxidase antibodies were elevated in two patients who could afford to pay for the tests.

The other group of patients managed for hypothyroidism included six patients (three males and three females) with multiple anterior pituitary hormone deficiency. Four patients had confirmed growth hormone deficiency and two males presented with associated micropenis. Although there were no overt symptoms and signs of adrenal insufficiency, only three patients had enough funds to rule out associated adrenal insufficiency before the commencement of levothyroxine therapy.

All the patients with CH were commenced on levothyroxine tablets at a dose of 10 μg/kg by mouth once daily aiming to normalize serum TSH and maintain FT4 in the upper half of the reference range and adjusted subsequently as necessary. The patients with AH were commenced on levothyroxine tablets at a dose of 5 μg/kg once daily and dose adjusted to maintain a euthyroid state.

Other groups of disorders seen were euthyroid sick syndrome (ESS) and Graves' disease as summarized in Table 1. The two patients managed for ESS were a 16-month-old female with protein–energy malnutrition and a 3-month-old female infant with sepsis. Thyroid functions of the patients with ESS showed serum low FT3, FT4 on the lower limit of normal, and increased TSH. They were both treated with low-dose thyroxine (25 μg daily) which was discontinued on recovery about 4 weeks after discharge. Subsequently, at follow-up, the patients have remained euthyroid. One 9-year-old girl had a simple goiter with euthyroidism and another 7-year-old girl was managed for acute thyroiditis.

The analysis of the clinical profile and anthropometry of the nine female children with hyperthyroidism is shown in Table 2. The mean age at presentation was 9.4 ± 2.09 years. Eight (88.9%) patients were in the pubertal age range. The WAZ scores for the five patients aged below 10 years were computed and the median (range) was 0.36 (range: −0.46–1.16). The HAZ scores for all the patients were normal with a median (range) of 1.42 (range: 0.08–2.91). The median (range) BMIZ score was –1.9 (–3.11 to– 0.45). Six out of the nine (66.7%) had normal BMIZ scores, two (22.2%) patients had wasting while one patient (11.1%) had severe wasting. Clinical features in all the patients included goiter, weight loss, heat intolerance, exophthalmos, tremors, and tachycardia. Graves' disease was confirmed in five patients (55.6%) with elevated thyroid receptor antibodies who could afford to pay for the test. All the patients were treated with carbimazole which was started at the dose of 0.5 mg/kg/day in 2–3 divided doses and titrated to the lowest possible dose needed to maintain a euthyroid status in the patient. In addition, because of the features of severe cardiovascular hyperactivity such as palpitations and tachycardia in all the patients, they were also commenced on a β-adrenergic blocker, propranolol, at a starting dose of 0.5 mg/kg/day in 2–3 divided doses for varying duration of time.

Eight infants of mothers on treatment for hyperthyroidism (first seen between the 7th h of life to 2 months of age) had transient hypothyroidism while one who presented at the age of 8 days had a transient hyperthyroidism.

Discussion

The incidence of thyroid disorders in the current study was 1 per 1000 cases with a rate of 0.13%. This is comparable to

Table 2: Clinical profile and anthropometry of the patients with hyperthyroidism

Patient number	Age (years)	Weight (kg)	WAZ	Height (cm)	HAZ	BMI (kg/m^2)	BMI z-scores	Thyroid receptor antibodies
1	5.6	21.0	0.53	126.6	2.74	13.1	−1.64	Positive and increased
2	8.0	24.0	−0.38	135.7	1.40	13.0	−1.90	Positive and increased
3	8.7	32.2	1.16	148.0	2.91	14.7	−0.45	Positive and increased
4	13.0	37.0	N/A	157.2	0.08	15.0	−2.00	Not done
5	9.5	28.0	−0.46	146.0	1.60	13.1	−2.16	Positive and increased
6	8.5	29.0	0.36	144.0	2.34	13.7	−1.40	Not done
7	11.0	34.0	N/A	154.5	1.42	14.0	−1.89	Not done
8	10.0	25.0	N/A	140.0	0.13	12.8	−2.66	Not done
9	10.6	26.0	N/A	144.5	0.31	12.5	−3.11	Positive and increased

BMI – Body mass index; N/A – Not/Available; WAZ – Weight-for-age z-score; HAZ – Height-for-age z-score

the rates of 0.12% and 0.1% documented in recent reports by Onyiriuka *et al*.[6] and Jaja and Yarhere[7] from Benin and Port Harcourt, both in South-South Nigeria, respectively. This rate is, however, higher than the incidence of 0.07% reported in a previous Nigerian study by Laditan and Johnson[4] in Ibadan, South-West Nigeria, done about 40 years ago. The higher incidence rates of the index study and other relatively recent studies[6,7] may be related to more awareness about pediatric endocrine diseases in the country due to the development of the subspecialty in Nigeria and training of more medical personnel. With regard to the extent endocrine diseases contribute to the burden of pediatric consultations, the percentage of 1.03% in the present study is slightly higher than the rates of 0.72% in Benin and 0.2% in Ibadan, both in Nigeria,. In spite of these differences, the essential point is that, despite the huge burden of infectious diseases and nutritional disorders plaguing the region,[11] endocrine disorders occur in Nigerian children and provision for care is advocated at all levels of health care.

Thyroid diseases also constituted a significant proportion of the pediatric endocrine disorders. The proportion was similar to the report by Onyiriuka and Kouyaté[11] where it constituted about 12.1%. However, this percentage is lower than that recorded by Jaja and Yarhere[7] (29.3%) and Laditan and Johnson[4] (37%) while being higher that the proportion of 6.4% recorded by Jarret *et al*.[12] in Ibadan 33 years later after Laditan and Johnson.[4] Comparably also, it is reported that 12% of the United States population will develop a thyroid condition in their lifetime.[13] In spite of the varying proportions, it is clear that thyroid disorders constitute a significant burden of the pediatric endocrine disorders encountered and require attention.

There was a slight female preponderance in the cases seen in the index study as has been documented in many other studies[6,14,15] except the Port Harcourt study[7] in which the thyroid disorders seen were 1.7 times more common in males. The reasons for this difference are not immediately obvious but may be related to the age groups of the patients and the predominant specific thyroid disorders encountered in the various studies. The youngest patient reported in our study was seen at 7 h of age. However, the youngest age at presentation from other Nigerian studies[4,6,7] varied from 5 days to 4 months while another Indian study by Yelluri[14] recorded the youngest age at presentation as "<1 month." Variation in age at presentation may be related to the nonavailability of newborn screening for hypothyroidism and awareness among both health workers and the general populace in these settings. Furthermore, synergy between the physicians managing the pregnant mothers with thyroid disorders may affect how early the newborns of such mothers are screened for thyroid disorders.

The proportion of the patients managed for CH in the present study (46.7%) approximates that of 50% reported by Jaja and Yarhere.[7] Previous reports from Nigeria[6] and India[14] had also reported significant percentages of 22%, despite being lower. The main presenting features of poor growth, delayed development, and excessive sleepiness and sluggishness were also common in the above Nigerian studies.[6,7] Frequently, these patients are incidentally picked up when thyroid function tests are done in evaluation of these patients for developmental delay by the pediatric neurologists or the general pediatricians. Recurrent anemia in the absence of other common causes of anemia in our environment also necessitated screening and subsequent diagnosis of CH as has been noted by other authors.[7] Nonendemic CH is reported as one of the most common treatable causes of mental retardation.[16] Neonatal thyroid screening is a particularly sensitive monitoring tool in the evaluation of the effects and of the correction of iodine deficiency at the population level and has also proved useful in the elucidation of the prevalence of the various causes of CH.[16,17]

DS constituted about 45% of the total cases of the patients with CH in the current study. Even though the scope of this study did not determine the percentage of thyroid disorders among all the patients with DS in LUTH, previous studies[18,19] and more recent reports[20,21] have documented rates of overt hypothyroidism in patients with DS ranging from 7% to 23.5%. Furthermore, Fort *et al*.[22] had reported that persistent primary CH is 28 times more common in infants with DS than the general population of healthy newborns. Erlichman *et al*.[23] documented that T4-based screening does not identify many cases of CH in neonates with DS and therefore recommends that the screening approach to infants with DS should initially include simultaneous T4 and TSH because of the possibility of missing patients with

compensated hypothyroidism (i.e. that present with moderate TSH elevation sufficient to normalize FT4 concentrations), which neonates with DS frequently have at birth.[23]

An Italian study by Iughetti *et al*.[20] also noted that the probability of AH increased from 30% at birth to 49% at 10 years in patients with DS. In 2001, the American Academy of Pediatrics recommended annual thyroid screening tests as part of the health supervision for children with DS,[24] and a subsequent increase in the incidence of medically treated thyroid disease was reported after these guidelines were re-released.[25] In view of these observations coupled with the fact that some symptoms of hypothyroidism may mimic some symptoms related to the natural course of DS, it is recommended that children with DS should be screened annually for thyroid function. Careful follow-up is also necessary to prevent further deterioration of their mental development or growth.[18,20-25]

In contrast to the present study, there were no cases of DS among the patients with thyroid problems in previous Nigerian studies.[4,6,7] This difference may be related to the fact that, in the recent years, screening for thyroid function with serum-free T4, serum-free T3, and TSH has become routine in the management of patients with DS presenting to any of the pediatric clinics of LUTH facilitating detection. It is also noteworthy that more than half of the patients with DS in the index study had associated congenital heart defects. Higher proportions of 73.6% and 62.5%, respectively, have been documented by Unachak *et al*.[18] and Purdy *et al*.[19] However, there was no statistical correlation between the co-existence of cardiovascular anomalies in DS and incidence of CH or subclinical hypothyroidism in these reports.[18,19]

AH constituted a similar proportion to the 10% reported by Jaja and Yarhere.[7] This is, however, lower than the percentage of 47.5% documented by Yelluri.[14] Both goitrous (Hashimoto thyroiditis) and nongoitrous (atrophic thyroiditis) variants of chronic lymphocytic thyroiditis are common causes of AH.[16] The most common age at presentation is adolescence, but the disease may occur at any age,[16] as seen in our study where the age ranged from 3 to 13 years. However, because of financial constraints and lack of health insurance services for extensive investigations as also encountered by Jaja and Yarhere[7] in similar "resource-constrained" settings, it was difficult to determine the specific causes and course of these acquired thyroid disorders except in three out of ten patients in the index study. A review of the epidemiology of thyroid diseases in Africa by Ogbera and Kuku[15] had also noted that the scope of antibody profiles in cases of suspected autoimmune thyroid diseases in Africa is unknown because the focus of management is treating clinical manifestations with the available meager resources rather than carrying out in-depth investigations.

The patients with hypothyroidism associated with MAPHD in the present study probably had TSH deficiency. Reports indicate that such TSH deficiency may be isolated or associated with other pituitary hormone deficiencies especially growth hormone.[16] Secondary or tertiary hypothyroidism in less severely affected children with the congenital abnormalities may be recognized only later in childhood[16] as was encountered in patients in the index study who presented between the ages of 4 and 14 years.

Two patients had ESS in the present study. Acute and chronic illnesses can cause alterations in thyroid hormone economy in the absence of an underlying intrinsic thyroid disorder.[26,27]

The percentage of patients with hyperthyroidism in the current study is similar to the rate of 11.1% reported by Yelluri.[14] This is lower than the rates of 27.8%–66.7% documented in previous Nigerian studies[4,6,7] but higher than the rate of 2% documented by Desai[24] in India. These differences might be related to the specific causes of hyperthyroidism and genetic and environmental influences in the various studies.

More than 95% of cases of hyperthyroidism are due to Graves' disease,[16] the predominantly documented of the autoimmune diseases of the thyroid gland in Africa,[29] with a strong female predisposition,[16] as was noted in the index study. It is also common in adolescence as only one prepubertal patient was seen fortunately because prepubertal children tend to have more severe disease, to require longer medical therapy and to achieve a lower rate of remission as compared with pubertal children.[16] Even though the ophthalmopathy characteristic of Graves' disease in adults is said to be considerably less common in children,[16] all the children seen in the present study as well as previous Nigerian studies[4,6,7] had significant exophthalmos at presentation. It is not immediately obvious whether this common occurrence is related to long duration of symptoms and late presentation or some racial predilection. Further studies are needed to elucidate this observation.

Transient neonatal hypothyroidism may develop in babies whose mothers are being treated with antithyroid medication or when maternal TSH receptor-blocking antibodies cross the placenta to the fetus intrauterine[16] as was documented in the current study and in a previous Nigerian study.[7] Replacement therapy is not usually required. Usually, the hypothyroidism resolves in 3 or 4 months. Conversely, transient neonatal hyperthyroidism which occurred in one of the babies born to a mother with Graves' disease almost results from the transplacental passage of maternal TSH receptor-stimulating antibodies.[16] Similarly, a more affected infant was managed for transient neonatal thyrotoxicosis in the report by Jaja and Yarhere.[7]

A limitation of the present study was the nonavailability of extensive investigations, especially in the cases of suspected autoimmune disorders of the thyroid to fully document the pattern of predominant antibodies.

In conclusion, pediatric thyroid disorders are common and CH constituted a majority. In view of the preventable mental retardation that can occur if not treated promptly, newborn screening is advocated in the country. Meanwhile, clinicians

should maintain a high index of suspicion for CH. Newborns of mothers with thyroid illnesses should also be screened and followed up for optimal results.

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Conflicts of interest

There are no conflicts of interest.

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