Short Communication

Pattern and Predictors of Thyroid Dysfunction among Pediatric Endocrine Referrals at the Tertiary Care Center of Northern India: A Longitudinal Study

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Abstract

Postiodization era has experienced a change in pediatric thyroid disorders with autoimmune disorders and subclinical hypothyroidism (SCH) now more frequently diagnosed. The aims of this study were to evaluate the clinical spectrum of thyroid disorders among children referred to us, to ascertain characteristics that influence treatment, and to follow them for various outcome measures. An observational longitudinal study where all treatment-naïve children (<18 years) with suspected thyroid disorders were recruited. Data collected were anthropometry, serum TSH, TT4, TT3, antithyroid autoantibodies, family history, and clinical symptoms. The management was based on the clinical judgment of the endocrinologist with the first follow-up at six weeks and subsequent visits three monthly for one year. A total of 241 subjects aged 28 days to 17 years were included. Overall, SCH was the most common abnormality (39%) detected among subjects, followed by overt hypothyroidism (OH) (33%), congenital hypothyroidism (CH) (18%), and overt thyrotoxicosis (5%). A total of 85.5% ($n = 204$) of subjects were treated and in follow-up, 81% of them were found to be adequately managed. Comparative analysis of OH and SCH revealed pubertal age, female predominance, and the presence of autoimmunity (positive anti-TPO and anti-TG Ab) statically significant variables in the OH group. A major independent predictor of treatment in treated SCH (72/96) in comparison with nontreated SCH (24/96) was anti-TPO positivity ($P = 0.029$). Eight of 24 nontreated SCH were eventually treated in follow-up and positive family history was observed as a significant variable among them ($P < 0.05$). Subjects with CH presented at a mean age of 6 months (28 days to 2 years). However, guidelines for the management of SCH are still evolving, autoimmunity and positive family history should be considered as decisive factors while initializing treatment. Delayed presentation of CH in our study warrants active surveillance of children at birth for thyroid disorders for their mental well-being.

Keywords: Goitre, pediatric thyroid disorders, subclinical hypothyroidism

Introduction

Disorders of the thyroid gland are among the commonest endocrine disorders worldwide. During infancy and childhood, functional abnormalities of the thyroid gland can adversely affect skeletal growth and brain maturation.

After the successful implementation and widespread coverage of the National Iodine Deficiency Diseases Control Program (NIDDCP) in India,[1] there has been a gradual transition between the pattern and prevalence of thyroid disorders in the pediatric population. Congenital hypothyroidism, the most common preventable cause of mental retardation, is still observed at a higher frequency in India in comparison with worldwide prevalence.[2] The postiodization era has observed an increase in the prevalence of subclinical hypothyroidism with underlying autoimmunity more extensively described.[3,4] Few studies have been done till yet to study the outcome of such children diagnosed with some thyroid abnormalities regarding their treatment and follow-up, especially when the abnormalities in thyroid function (TFTs) are rather mild.[5]

Access this article online

Quick Response Code:

Website: www.ijcm.org.in

DOI: 10.4103/ijcm.ijcm_191_22

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How to cite this article: Sood M, Bhat MH, Masoodi SR, Ahmad PO. Pattern and predictors of thyroid dysfunction among pediatric endocrine referrals at the tertiary care center of Northern India: A longitudinal study. Indian J Community Med 2024;49:764-70.

Received: 23-02-22, **Accepted:** 29-02-24, **Published:** 03-07-24

Kashmir Valley has been an endemic zone for iodine deficiency disorders in the past;[6] however, recent surveys conducted by Masoodi *et al*. in 2013[7] showed marked improvement in overall iodine nutrition in Kashmir Valley two decades after the implementation of salt iodization. On the other hand, there have been no studies analyzing the changing patterns and prevalence of pediatric thyroid disorders postiodization in this region. Hence, this study aimed (1) to evaluate the pattern of abnormal thyroid function among Kashmiri children referred to our pediatric endocrine unit with various thyroid disorders and (2) to ascertain historical, clinical, and laboratory characteristics that influence treatment decisions. Moreover, we followed these children with appropriate therapy to study various outcome measures, particularly response to therapy.

One of the implicit benefits of this study was to audit the quality of pediatric endocrine services and to enhance good medical practice in the region.

Materials and Methods

This was a prospective observational study conducted from December 2016 to December 2018 with a one-year recruitment phase and a one-year follow-up phase. All assenting children and adolescents, aged 18 years or less, who referred or visited the pediatric endocrine OPD at our tertiary care center for suspected thyroid disorder (clinical or biochemical) and who were treatment-naive were recruited. The study was carried out as per the Declaration of Helsinki (2013), after ethical clearance was obtained from the Institutional Ethics Committee (IEC). Written informed consent was taken from parents or legal guardians along with the assent of the study subject before recruitment.

Those children, who were already on treatment for their thyroid problems, had a drug history known to alter the thyroid hormone status, or were critically sick were excluded from the study. A total of 300 children were initially included in our study and scrutinized as per the exclusion criterion, a total of 241 children were finally included in this study as shown in the flowchart. These study subjects were divided into four major groups as per age (0–2 years, 2–6 years, 6–12 years, 12–18 years) for further clinical assessment.

Clinical assessment

An in-depth assessment of each recruited subject was carried out. Demographic data and clinical history (indications for thyroid testing, reason for endocrine referral, the presence or absence of symptoms suggestive of thyroid disease, past medical history, or family history of thyroid illness) were recorded in a proforma. Anthropometric measurements were noted using IAP/WHO reference growth charts[8] and pubertal staging was done as per Tanner staging. Thyroid examination was done by palpation method and graded as per WHO classification.[9] Each child was scored by Zulewski's score (if symptoms/signs are suggestive of hypothyroidism), or by Waynes index (in case of suspected thyrotoxicosis).[9]

Laboratory evaluation

All study subjects were tested for total thyroxine (TT4), total tri-iodothyronine (TT3), thyroid stimulating hormone (TSH), antithyroid peroxidase (anti-TPO) antibody, anti-thyroglobulin (anti-TG) antibody, and complete blood count (CBC), irrespective of their previous reports. X-ray for bone age, ultrasonography neck, Technetium^{99} scan, perchlorate discharge test, and FNAC (fine needle aspiration cytology) were done as and when required. All assays (TT3, TT4, and TSH) were done by Beckman Coulter DxI-800 analyzer by chemiluminescence immunoassay. In clinically euthyroid individuals, subclinical hypothyroidism (SCH) was diagnosed if serum TT4 levels were normal (4.5–13 ug/dl) and serum TSH was elevated (6.5–10 μIU/ml), while subclinical thyrotoxicosis was diagnosed if low TSH (<0·1 μIU/ml) levels were detected in the presence of normal serum TT4 concentration. Overt hypothyroidism (OH) was diagnosed with low TT4 (<4.5 ug/dl) or high TSH (>10 μIU/ml) and overt thyrotoxicosis with high T4 levels (>13 ug/dl) and low TSH levels (<0·1 μIU/ml). Congenital hypothyroidism (CH) was diagnosed in subjects presenting with symptoms at age < 2 years with thyroid function test (TFT) as per age-specific criterion.[10] There was no case of secondary hypothyroidism and subclinical thyrotoxicosis.

Management and follow up

The decision to start therapy or to manage conservatively was based on the clinical judgment of the attending endocrinologist. The first follow-up visit was done at six weeks with subsequent visits at 3-month interval as per our pediatric thyroid clinic protocol. During each visit, besides clinical examination, TT3, TT4, and TSH measurements were done in all subjects. At the end of the study period, management adequacy was judged by assessing the frequency of euthyroidism maintained in follow-up for one year. Those subjects, who had four regular visits and were euthyroid in the last two consecutive visits whether on treatment or not, were considered adequately managed.

Statistical analysis

Statistical analyses were conducted using commercially available statistical software. Data was first keyed into MS Excel™ and cleaned before importing into the statistical software. Pearson's Chi-square test and Fisher's exact test evaluated differences between categorical variables as appropriate. Student's *t* test was used to test for differences between continuous variables. Wilcoxon rank-sum test was used to test for differences between continuous variables with nonparametric distributions. A two-tailed *P* value of < 0.05 was considered significant. Results were expressed as an odds ratio (OR) with 95% confidence interval (CI), mean ± standard deviation (SD), or median [inter-quartile range].

Results

A total of 241 children with clinical or biochemical suspicion of thyroid disorders were included in the study. The overall age

of the referred subjects ranged from 28 days to 17 years with a mean of 7.19 ± 4.72 years (median = 7). Females outnumbered males with a female-to-male ratio of 1.67:1. Patients were referred to us with a wide spectrum of clinical and biochemical abnormalities related to thyroid and the most common among the biochemical abnormalities was elevated TSH (80%) as shown in Figure 1. The most common symptoms among these children for which the initial evaluation was done were constipation (23.7%) followed by pain lower extremities. Goiter was detected in 36.5% (n = 88) of subjects with significantly higher prevalence in the pubertal age group (n = 24, 27.3%) and females outnumbered males (70.5% vs 29.5%; $P < 0.05$). Family history of thyroid illness was positive in 53% of subjects (n = 130). Study subjects were classified into five groups after their repeat thyroid function test (TFT) as shown in the flow chart [Figure 2]. Among the hypothyroid cohort, 55% (n = 96) were having SCH and the remaining had OH (n = 80). CH was observed in 18% (n = 45) subjects, 5% (n = 12) subjects had overt thyrotoxicosis (OT), and the rest were euthyroid (n = 8). The baseline characteristics of subjects in each group are shown in Table 1. Three children diagnosed with Down's syndrome presented to us with congenital hypothyroidism. Pendred syndrome was diagnosed in one child after a detailed evaluation. After the initial evaluation, out of a total of 241 subjects, 204 were treated while 37 subjects were managed conservatively [Figure 2].

Referral for evaluation of hypothyroidism

Overall, 176 subjects were diagnosed with hypothyroidism with 55% of subjects having SCH.

Comparative analysis of OH and SCH

There was a significant difference in clinical and biochemical parameters between OH and SCH groups as shown in Table 2. Besides the mean age of presentation and proportion of females, both groups differed significantly in the presence of autoimmunity markers (anti-TPO and anti-TG) with a higher number of overt hypothyroids antibody positive. The mean dose requirement of SCH was significantly lower than the OH group (2.2 + 1.139 ug/kg/day vs 1.75 + 1.07 ug/kg/day; $P < 0.003$). Although in SCH three-fourths of subjects were treated (n = 72/96) in comparison with the OH group where all subjects were treated, there was no significant difference in management adequacy judged at the end of follow-up in both groups ($P > 0.05$) as shown in Table 2.

Comparative analysis of treated versus nontreated subclinical hypothyroids

When we compared the clinical and biochemical parameters of treated versus nontreated SCH, the three major variables differed significantly. Besides mean age and height SDS, anti-TPO antibody levels emerged as a significant variable between treated and nontreated groups as shown in Table 3. The rest of the parameters were comparable in both groups. There was a significant difference in initial clinical presentation in both groups. Neck swelling complaint was exclusively observed in the treated SCH group (n = 13; $P < 0.01$), while pain in extremities or routine evaluation was the predominant reason for initial evaluation in the nontreated SCH group ($P < 0.05$). The rest of the parameters (presence of goiter, antibody levels, mean TSH, and age of presentation) differed nonsignificantly in both groups as shown in Table 4.

Eight subjects with nontreated SCH (n = 8/24) were treated in follow-up [Figure 2]. The specific feature observed in this group when analyzed retrospectively was the positive family history observed in 75% (n = 6/8) subjects compared to those who were conservatively managed (n = 5/16, 31.3%); P = 0.043.

Referral for evaluation of congenital hypothyroidism

Overall, 45 subjects were diagnosed with congenital hypothyroidism after the initial evaluation. Baseline characteristics of the subjects are shown in Table 1. Only two children were diagnosed in the neonatal period, the rest were diagnosed postneonatal period with mean age of presentation 6 months. Imaging (ultrasonography, thyroid scanning, and perchlorate discharge test) was possible in 29 subjects. Hypoplasia and dyshormonogenesis of the thyroid gland were the most common etiology observed in 20% of subjects. Autoimmune markers were positive in nine subjects (28.8%). All subjects were started on treatment after the initial evaluation. Follow-up regarding adequacy of treatment revealed 82.2% of subjects were adequately managed [Table 1].

Referral for thyrotoxicosis

Twelve subjects were diagnosed with thyrotoxicosis. All except one were diagnosed with Graves' disease (n = 11) and one-third of these subjects had evidence of orbitopathy (n = 4). The mean age of presentation of this cohort was 12.68 ± 4.06 years with females affected predominantly (91.1%). All patients with Graves' disease were started on antithyroid drugs, and at the end of the study, all except one were found to be adequately managed

Discussion

Among the 241 children included in our study, most of them had

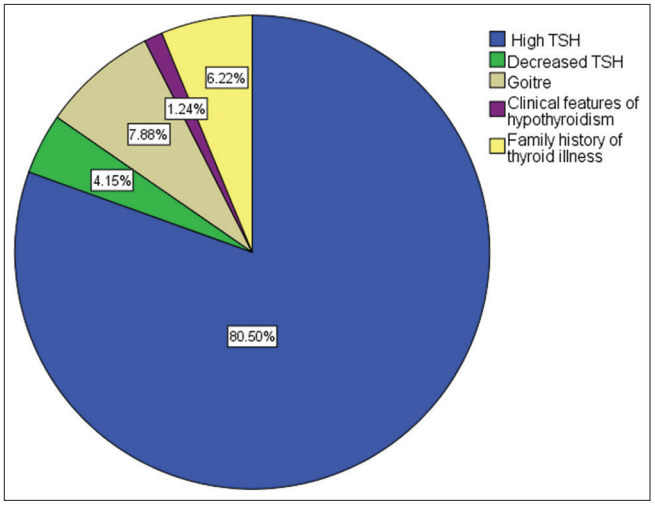

Figure 1: Pie charts showing the various TFT abnormalities for which endocrine referral was made

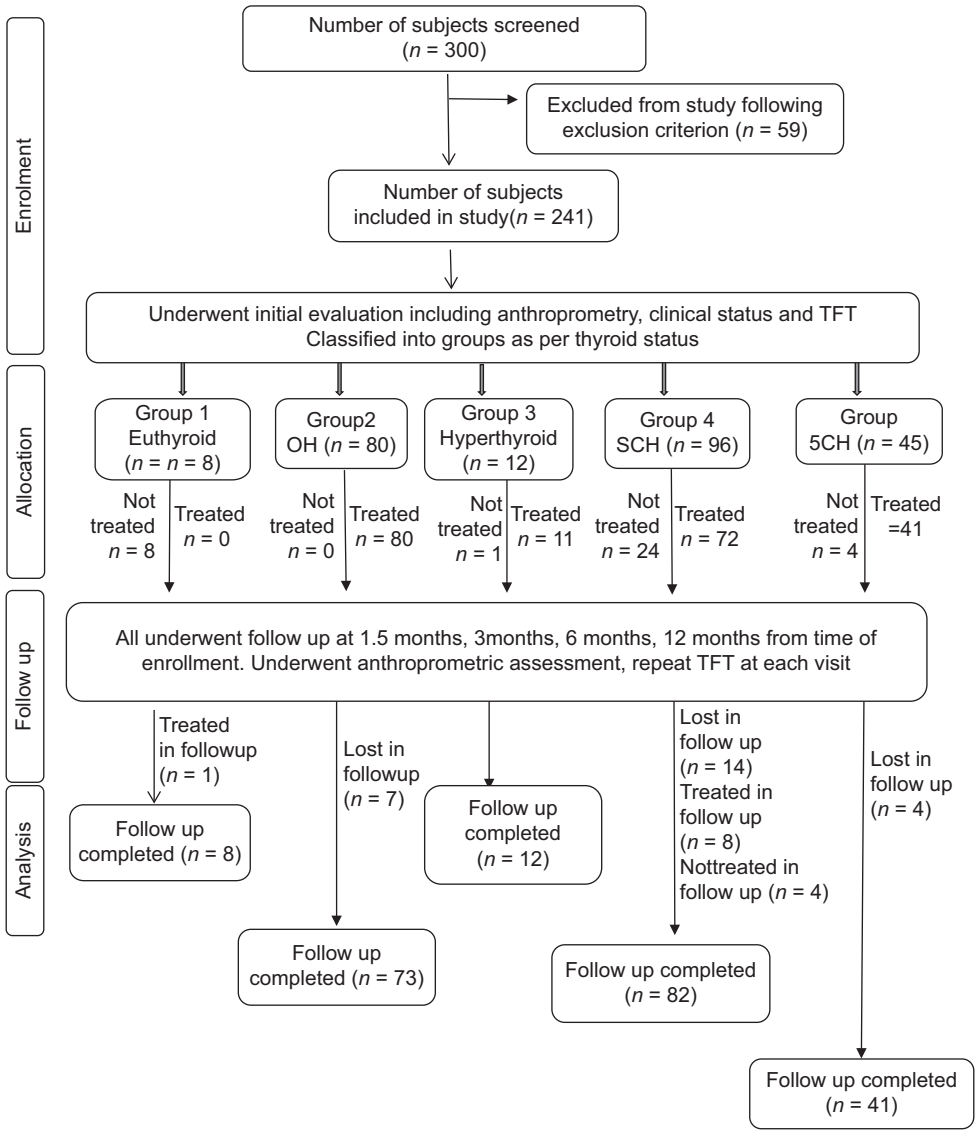

Figure 2: CONSORT chart depicting the flow of the patients throughout the study

Table 1: Baseline characteristics of the subject as per their thyroid status

Variables	Euthyroid (*n*=8)	Overt hypothyroidism (*n*=80)	Subclinical hypothyroidism (*n*=96)	Congenital hypothyroidism (*n*=45)	Thyrotoxicosis (*n*=12)
Mean age±SD (range) years	8.25±5.00 (2.2–14)	9.57±3.65 (2.3–17)	8.45±3.52 (2.1–16)	0.841±0.49 (0.08–2)	12.68±4.064 (5.7–16)
F:M*	1:1	1.25:1	1.13:1	1.04:1	11:1
Family history positive	62.5% (*n*=5)	56.3% (44)	50% (*n*=48)	64.4% (*n*=29)	33.3% (*n*=4)
Presence of goiter	50% (*n*=4)	43.8% (35)	37.5% (*n*=36)	4.4% (*n*=2)	91.7% (*n*=11)
Anti-TPO positive (%)	12.5% (*n*=1)	61.3% (*n*=49)	31.3% (*n*=30)	13.3% (*n*=6)	83.3% (*n*=10)
Anti-TG positive (%)	12.5% (*n*=1)	45% (*n*=36)	21.9% (*n*=21)	6.7% (*n*=3)	66.7% (*n*=8)
Management adequacy	100% (*n*=8)	71.3% (*n*=57)	64.6% (*n*=81)	82.2% (*n*=37)	91.7% (11)

*F: Female, M: Male

been referred to a higher center for evaluation and management of elevated TSH. SCH was the most common thyroid function abnormality elicited among them (96/176). The majority of these children had been investigated by a pediatrician for vague complaints like constipation and easy fatigability. Routine screening was cited as the reason for evaluation in 7% of subjects. Frequent thyroid function testing because of low cost, widespread availability, and vague presentation of thyroid dysfunction has led to a high detection rate of subtle abnormalities in thyroid function which merits judicious management.

Table 2: Comparative analysis of clinical and biochemical parameters of overt and subclinical hypothyroid group

	Overt hypothyroid (*n*=80)	Subclinical hypothyroid (*n*=96)	*P*
Age, mean±SD (years)	9.57±3.65	8.45±3.52*	0.041
Females (%)	62 (77.5)	51 (53.1) *	0.001
Height SDS, mean	0.31±0.73	0.26±0.71	0.646
BMI Z score, mean±SD	0.144±0.512	−0.69±1.12	0.210
Presence of goiter (%)	35 (43.8)	36 (37.5) *	0.400
Positive family history (%)	44 (55.7)	48 (50)	0.453
Anti-TPO Ab positive (%)	49 (61.3)	30 (31.3) *	0.001
Anti-TB Ab positive (%)	36 (45.0)	21 (21.9) *	0.001
Presence of anemia (%)	15 (27.8)	9 (15.5)	0.114
Median TSH (uIU/ml) (range)	63 µIU/mL (10.1–775)	9.59 µIU/ml (6.6–10)	
Adequate management (%)	57 (78.1)	62 (76.5)	0.820
Dose (ug/kg/day) mean±SD	2.20+1.139	1.75+1.07*	0.003

Table 3: Comparative analysis of treated versus nontreated subclinical hypothyroid

	Treated (*n*=72)	Nontreated (*n*=24)	*P*
Age, mean±SD (years)	9.05±3.69	6.65±2.17*	0.003
Females (%)	39 (54.2)	12 (50.0)	0.723
Height SDS, mean±SD	0.36±0.74	−0.32±0.54*	0.018
BMI Z score, mean±SD	0.178±1.22	−0.33±0.65	0.189
Presence of goiter (%)	30 (41.7)	6 (25)	0.144
Positive Family history (%)	37 (51.4)	11 (45.8)	0.637
Anti-TPO Ab (U/L) (%)	26 (36.1)	3 (12.5)*	0.029
Anti-TG Ab (U/L) (%)	17 (23.6)	4 (16.7)	0.476
Presence of anemia (%)	6 (14.6)	3 (17.6.5)	0.114
TSH (uIU/ml) mean±SD	9.29±0.88	8.93±1.02	0.103
Adequate management (%)	46 (75.4)	13 (56.5)	0.091

Table 4: Comparative analysis of clinical features at the time of referral in treated and nontreated groups of subclinical hypothyroid

Clinical features	Treated SCH (*n*=72)	Nontreated SCH (*n*=24)
Constipation (%)	17 (23.6)	5 (20.8)
Neck swelling (%)	13 (18.1)	0 (0)*
Short stature (%)	6 (6.3)	3 (3.1)
Fatigue (%)	12 (16.7)	2 (8.3)
Routine evaluation (%)	0 (0)	2 (8.3)*
Weight gain (%)	7 (9.7)	1 (4.2)
Pain extremities (%)	5 (6.9)	7 (29.2)*
Family history (%)	1 (1.4)	2 (8.3)

*P<0.05. Overall there was a significant difference in clinical features at the time of presentation in treated vs nontreated SCH with P<0.01

Similar trends have been observed by other clinicians analyzing the spectrum of pediatric thyroid disorders worldwide. Lahoti *et al*.[11] in 2016 did a retrospective analysis of 230 pediatric endocrine referrals and found that only 20% of the patients referred to rule out hypothyroidism had true thyroid dysfunction. The majority of children were referred with elevated TSH as like in our study, but follow-up TSH done after six—eight weeks was normal in over 50% of patients.

Clinical spectrum of hypothyroidism in children

Overt hypothyroids in our study (80/176) were all started on treatment after initial evaluation. Autoimmunity (positive anti-TPO and anti-TG Ab) seemed to be an important etiological factor in this group and was significantly higher than the subclinical hypothyroid group. High goiter prevalence was likely due to referral bias and a strong family history in the OH group corroborates with other similar studies.[12,13]

However, there are few pediatric studies looking at the outcomes of subclinical hypothyroid children treated with l-thyroxine versus those given a placebo but in the absence of clear-cut guidelines regarding diagnosis and management confusion prevails.

Currently, there is little evidence to recommend treatment in most children with SCH in whom serum TSH is <10 mIU/ML with TT4 or FT4 in normal limits.[14] The major concern that leads to overdiagnosis and enthusiastic treatment of SCH is growth concerns, especially in pubertal years. Cetinkaya *et al*.[15] in their prospective study of 39 patients with short stature and SCH showed that both prepubertal and pubertal patients experienced a significant improvement in growth after 6–12 months of treatment with L-thyroxine although the study duration is short to assess actual height improvement. Contrary to this, Cerbone *et al*.[16] in longitudinal follow-up of 36 children with SCH and 36 age- and sex-matched healthy children revealed that untreated long-standing SCH was not associated with deterioration in growth and bone maturation. Therefore, when deciding on treatment modality in children with SCH and short stature, the expected benefits should be weighed against the side effects of long-term treatment.

A total of 75% of SCH in our study were treated although at the end of one year of follow-up, the management was found to be adequate in both treated and untreated SCH groups. This

is really a thought-provoking fact because the majority of SCH receive investigation-based treatment rather than clinical assessment-based treatment. We compared the clinical and biochemical parameters of the treated versus nontreated SCH group. Treated groups were in their initial pubertal years in comparison with the nontreated group who were prepubertal and secondly had high positivity for anti-TPO antibody levels. Increased requirement of thyroid hormones in pubertal years and higher chances of conversion of subclinical to overt hypothyroidism in those with anti-TPO antibody positivity[17,18] seemed to be decisive factors for starting treatment in SCH-treated group. Besides this, the clinical presentation also varied in both groups and the complaint of neck swelling seemed to be an important detrimental factor for starting treatment. Although height SDS varied in treated and nontreated SCH at the beginning but to reach conclusive evidence of the beneficial effects of L thyroxine on height, we need long-term follow-up which was lacking in our study. Another interesting observation made in the follow-up of these nontreated SCH groups was that one-third of them (8/24) were started on treatment in follow-up due to the progressive increase in TSH. An important discriminatory feature among these patients was the presence of a family history of thyroid illness. Thus, the presence of family history can be considered an important decisive factor in initiating treatment in the SCH group as shown by Such *et al*.[19] in 51 subclinical hypothyroid children. In his retrospective analysis of the SCH cohort from 2009 to 2014, besides the presence of family history, no difference between treated and nontreated groups was observed regarding age, TSH concentration, BMI *Z*-score, and height SDS values.

The pattern of thyroid dysfunction in children less than 2 years in our study revealed a delayed diagnosis of hypothyroidism in this sensitive group as only two children were referred to us at age less than one month, the rest being diagnosed at a mean age of 6 months. Lack of a nationwide screening programs results in delayed diagnosis of hypothyroidism in the early years, thus affecting both the neurological and physical well-being of children. Desai *et al*. and similar studies from India[19-21] have reported a higher incidence of congenital hypothyroidism (1:2500–2800 live births) in comparison with worldwide incidence (1 in 3800).[12] Other Indian studies have also shown that less than 10% of cases of congenital hypothyroidism are diagnosed by the age of 3 months and only about 50% by the age of 2 years.[20,21] Lack of awareness among primary healthcare practitioners and along with varied clinical presentation of congenital hypothyroidism is the major reason behind this epidemiology. Thus, strengthening the screening programs and creating awareness regarding the varied spectrum of congenital hypothyroidism will promote the overall well-being of these children.

Prevalence and management of thyrotoxicosis

Although the proportion of thyrotoxic children in our referral cohort was small (5%), adequate management (91.7%) was the major highlight of this group. All except one were adequately treated with antithyroid drugs with no reported major side effects. The only case of an adolescent female with persistent hyperthyroidism was rendered euthyroid by radioactive iodine ablation in follow-up.

Limitations of our study

There are a few drawbacks to our study. Primarily it is an observational study and the decision to treat relies on the clinical acumen of the treating endocrinologist. Secondarily, because of time constraints, we could not pursue our study beyond one year to see the actual effectiveness of the treatment on the weight and height of the children treated. We expect to further conduct a long-term prospective study with a similar type of cohort to overcome these drawbacks.

Conclusions

Our study is real-world evidence analyzing the spectrum of pediatric thyroid disorders in the postiodization era and auditing their overall management in follow-up. SCH was the most common thyroid function abnormality in our study, and though three-fourths of these subjects were treated all were found to be adequately managed at the end irrespective of treatment status. Among children diagnosed with SCH, autoimmunity and a positive family history led to an increase in TSH in follow-up. An effective plan should be drafted to include TFT as a nationwide newborn screening program to prevent delayed diagnosis of congenital hypothyroidism hampering their mental and physical well-being. Future similar long-term real-world studies will help in establishing authentic guidelines regarding the management of pediatric thyroid disorders.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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