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ETIOLOGICAL PROFILE OF GOITER AND CORRELATION BETWEEN IODINE NUTRITIONAL STATUS WITH AUTOIMMUNE THYROIDITIS IN CHILDREN

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Abstract : Despite years of salt iodization, goiter continues to be a major public health problem worldwide. Iodine intake has a marked influence on the incidence and prevalence of thyroid abnormalities in a population and excess iodine exposure was reported to be associated with autoimmune thyroiditis (AIT) and thyroid dysfunction. Measurement of urinary iodine excretion (UIE) reflects a persons iodine nutritional status and WHO recommend it to be used as the primary impact indicator for monitoring salt iodisation programme.AIM a. To evaluate for possible etiologies of goiter in children using a standard approach and b. To assess iodine nutrition and to correlate iodine nutritional status with autoimmune thyroiditis in children.MATERIALS AND METHODSDESIGN Descriptive studySTUDY PERIOD January 2010 to May 2011,STUDY POPULATION All children with goiter during the study period between age group 6-12 yrs, attending the pediatric endocrinology outpatient department of our institute. Children with proven congenital hypothyroidism were excluded from the study.MANOUVERE 59 Children with goiter were enrolled in the study. All 59 children were subjected to blood tests for T4, TSH, thyroid microsomal, antithyroglobulin antibody titres and Fine needle aspiration (FNAC). Urinary iodine excretion (UIE) was estimated in spot urine samples. RESULTS Among the various etiologies of goiter, autoimmune thyroiditis 42(71.2) was the commonest, followed by euthyroid goiter 13(22) and iodine deficiency 4(6.8) being the least. mild IDD was present only in 4 (6.8) children, 11 (18.6) had adequate iodine nutrition 17 (28.8) had UIE above normal requirements and 27(45.8) children had UIE more than 300ugL. The levels of urinary iodine were significantly higher in children with autoimmune thyroiditis compared with euthyroid goiter (316.9586.124 vs.167.94 58.72, p0.001).CONCLUSION In any child presenting with goiter complete work up is necessary, so as to decide upon a rational treatment. A possible link between increased iodine intake and autoimmune thyroiditis was found in our study.

Keyword :urinary iodine, autoimmune thyroiditis, euthyroid goiter,subclinical hypothyroidism

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INTRODUCTION:

Iodine deficiency in endemic areas and autoimmune thyroiditis in iodine sufficient regions are the major etiological factor for goiter. Goiter rate is 13.5% in Tamilnadu despite salt iodization (1). These observations necessitated the need to evaluate the etiology of residual goiter in post iodization phase. Following the implementation of National Iodine Deficiency Disorders Control Programme (NIDDCP) based on Universal Salt Iodization (USI), there are reports of normalization of iodine nutrition as reflected by urinary iodine excretion (UIE) in the country (2,3) According to current recommendations produced by the World Health Organization (WHO), median urinary iodine concentration of 100-199 ug/l in samples from school children indicate adequate iodine intake and optimal iodine nutrition (4) The urinary iodine concentration is the primary indicator of a person's iodine nutritional status and the primary variable used to measure the success of iodine supplementation in a population.(5)

OBJECTIVE:

To evaluate for possible etiologies of goiter in children using a standard approach andTo assess iodine nutrition and to correlate iodine nutritional status with autoimmune thyroiditis in children.**METHODOLOGY: DESIGN**: Descriptive study **STUDY PERIOD**: January 2010 to May 2011, **STUDY POPULATION**: All children with goiter during the study period between age group 6-12 yrs, attending the pediatric endocrinology outpatient department of our institute. Children with proven congenital hypothyroidism were excluded from the study.

MANOUEVRE: The study was initiated after institutional ethical committee approval. History regarding family history of thyroid disorders and iodized salt intake was elicited. Goiter was screened by palpation method and was graded as per the definition provided by WHO/ UNICEF/ICCIDD (4). The grading is described as Grade-0, no palpable or visible goiter; Grade-1, goiter that is palpable but not visible when the neck is in the normal position; and Grade-2, visible goiter when the neck is in the normal position. Those found to have goiter were subjected to blood tests for total T_4, TSH, thyroid microsomal antibody (TMA), and thyroglobulin antibody (TGA), as well as urinary iodine estimation in spot samples. FNAC was advised for all subjects. The clinical examination and investigations were performed after obtaining an informed consent. The stained slides were reported blindly by a cytopathologist, who had no access to clinical and serological data. The criteria adopted for the diagnosis of juvenile lymphocytic thyroiditis were: the presence of lymphocytic infiltrate, diminished colloid and minimal to moderate follicular destruction, with or without Hürthle cell change (6). T4 and TSH were estimated by ELISA method. The normal range of T4 as standardized in our lab was 51-154 nmol/L, for TSH 0.5-5mIu/mL Thyroid antibodies were tested by electrochemiluminescence assay (Cobas-Roche-Elecys 1010 analyser) where antimicrosomal antibody titers more than 34 Iu/mL, and antithyroglobulin antibody titers more than 115 Iu/mL for were considered significant. Spot urine samples were collected in a wide mouthed iodine free plastic container with tight screw tops

and kept in a refrigerator at -4°C after addition of 1 drop of toluene. Urinary iodine was estimated by ammonium per sulphate method. (3) **Definition**: **Juvenile autoimmune thyroiditis** (JAT) was diagnosed if the cytopathological features were consistent with lymphocytic thyroiditis or with significant elevation of anti-microsomal and anti-thyroglobulin antibodies. **Euthyroid goiter** (simple, diffuse non-toxic) where there is no clinical or laboratory evidence of thyroid dysfunction with negative antibody titres and normal UIE. Children with reduced UIE are labeled as iodine deficiency.

Subclinical hypothyroidism was diagnosed if serum T_4 levels were normal and serum TSH was elevated (>5 IU/mL), whereas subclinical hyperthyroidism was diagnosed if low TSH (<0.1 IU/mL) levels were detected in the presence of a normal T_4 concentration. **Overt hypothyroidism** was diagnosed with low T_4 (<51 nmol/L) and high TSH (>5 IU/mL) and **overt hyperthyroidism** by high T_4 levels (>154 nmol/L) and low TSH levels (<0.1 IU/mL).

Statistical analysis: Data was entered using Microsoft corp. excel and analyzed using SPSS version 16. Mean with standard deviation and median were calculated for continuous data. For skewed data Mann-Whitney U test was used to compare difference between means. Correlation between variables was done and Pearson Correlation Co-efficient was calculated. All tests were considered statistically significant at $p<0.05$.

RESULTS:

There were totally 59 cases of goiter in this study. The mean age of goiter presentation was 9.7 years .Goiter was seen more commonly in the 9-12 yrs age group and more common in girls with female to male ratio of 4:1. All our children presented with diffuse goiter. 23 (39%) had grade 1 and 36 (61%) had grade 2 goiter. Parents of 49 (83%) children knew they used iodized salt in their houses and 14 (23.7%) knew iodized salt prevents goiter. No family history of thyroid disease was reported in the study population. 3(5.1%) children had TSH values < 0.5miu/mL, 17 (28.8%) children had TSH values between 0.5 to 5 miu/mL, 39 (66.1%) children had TSH values > 5 miu/mL The mean serum TSH was 18.68 miu/L (18.68$\pm$18.35) thus indicating that a large number of children had high TSH. Mean T4 was 58.96(58.96 $\pm$ 47.26). 22 %(n=13) were biochemically euthyroid, 66 % (n=39) had overt hypothyroidism, 11.9 %(n=7) had subclinical hypothyroidism and subclinical hyperthyroidism was detected in 5.1 % .None of the subjects had overt hyperthyroidism. FNAC was carried out in all 59 children participated in the study. It revealed findings consistent with chronic lymphocytic thyroiditis in 23 (39%) and colloid goiter in 36 (61%). Antibody titers were done in all 59 subjects in whom FNAC was done. It revealed positive antimicrosomal antibody in 7(17%), antithyroglobulin positivity in 12(29.3%) and both positive in 22(53.7%).

From(table :2) it is clear that mild IDD was present only in 4(6.8%) children , 11 (18.6%) had adequate iodine nutrition.17(28.8%) had UIE above normal requirements and 27(45.8%) children had UIE more than 300ug/L indicating excessive levels, known to cause adverse health consequences as per WHO epidemiological criteria.

From (Table: 3) it is evident that the levels of urinary iodine were significantly higher in children with autoimmune thyroiditis compared with euthyroid goiter (316.95+86.124 vs.167.94 +58.72, $p<0.001$).From (table.4) it

TABLE: 1 ETIOLOGY OF GOITER

ETIOLOGY	FUNCTIONAL STATUS		NUMBER (%)
AIT	a	Overt hypothyroidism	32 (54.2%)
	b	Subclinical hypothyroidism	7 (11.9 %)
	c	Subclinical hyperthyroidism	3 (5.1%)
Euthyroid goiter	Normal thyroid function		13 (22%)
Mild iodine deficiency	Normal thyroid function		4(6.8%)

Table: 2 Assessment of iodine nutrition in children based on UIE (ug/L)

MedianUIE	Iodine nutrition status	numbers	%
50-99	Mild iodine deficiency	4	6.8
100-199	Adequate iodine nutrition	11	18.6
200-299	Above requirements	17	28.8
>300	Excessive (adverse effect)	27	45.8

Table 3: Comparison of median UIE (ug/l) among AIT and euthyroid goiter

ETIOLOGY	UIE (ug/L)				Mann Whitney U test
	N (%)	Mean	Std. Dev	Median	P value
Autoimmune thyroiditis	42 (71.2%)	316.95	86.124	335.00	<0.001
Euthyroid goiter	17 (28.8%)	167.94	58.723	172.50	

Table 4 Cross table for AIT and UIE group

UIE	AIT				Total	
	POSITIVE		NEGATIVE			
	n	%	n	%	n	%
<300ug/l	15	35.7	17	100.0	32	54.2
>300ug/l	27	64.3	0	0.0	27	45.8
Total	42	100	17	100	59	100

Chi-Square Tests	Value	df	P- Value
Pearson Chi-Square	20.408	1	0.001

is evident that there is a strong association between excess UIE and autoimmune thyroiditis ($p < 0.001$).

DISCUSSION:

Conventionally, in goiter survey programmes, children in the age group of 6 to 12 yrs were included to avoid the influence of programme, thyroid autoimmunity has been considered as an important cause for persistence of goiter, similar to our observation (7).our study from an area of mild to moderate iodine deficiency shows that nearly 71% of the children who presented with goiter had autoimmune thyroiditis. This could only be the tip of the iceberg as this is a hospital-based and not a community based study. The observation of greater prevalence of goiter in the girls compared to the boys in our study is probably related to the difference in sex hormones and pubertal growth pattern among boys and girls (8).

Euthyroid goiter with normal urine iodine excretion was found in a subset of our study population. The exact etiology was not found but it can be explained by goitrogens or micronutrient deficiency. Our studypopulation was iodine sufficient as evidenced by normal median urinary iodine excretion, except for mild iodine deficiency noted in 6.8% of children.We applied both serological and cytomorphological criteria to diagnose autoimmune thyroiditis. Very few studies applied both these criteria for diagnosis (8). The fact that roughly 55% of patients with AIT are missed by either of the two diagnostic approaches justifies the need to apply both to diagnose this entity. It is recognized that antibody titers might change but cytomorphological features persist during the clinical course of AIT indicating the need to combine cytological and serological evaluation to diagnose AIT (9). In our study, 75 % of the children exhibited higher than optimal UIE.UIE was high in goitrous children with AIT. The high UIE of our study could reflect a trend with time of improved penetration after execution of universal salt iodization. If the iodine concentration in iodinated salt exceeds the production level concentration of 20-40ppm, as recommended by WHO, it may unmask the thyroid dysfunction in susceptible individuals (10). Further studies are needed to clarify whether the higher UIE in goitrous children with AIT is causally related to AIT or is due to the inability of the diseased thyroid to trap available iodine efficiently. A possible link between excess UIE and AIT has been established in our study. With higher prevalence of autoimmune thyroiditis in iodine sufficient areas (11) as well as following iodine prophylaxis (12-14) there is a suggestion that iodine ingestion increases thyroid autoimmunity. A recent study from our country showed association of UIE with subclinical hypothyroidism along with AIT (12). A recent report from China has shown similar results indicating that excess iodine could lead to impaired thyroid function (15). There are studies which did not find an association between urinary iodine and thyroid antibodies (7). The exact mechanism behind an iodine induced increase in incidence of AIT is unknown, but several hypotheses have been postulated. Excess iodine may lead to apoptosis of thyroid follicular cells as studied in (invitro) systems (16). Also chronic iodine excess induces apoptosis and necrosis of thyroid follicular and endothelial cells leading to thyroglobulin accumulation in connective tissue (17). High iodine intake, associated with infiltration of thyroid by lymphocytes in genetically susceptible mice,

may worsen the uptake defect of iodine thus decreasing thyroid hormone synthesis (19).Recently it was experimentally found that antioxidative protection may also be weakened by excessive iodine intake (20).
The role of iodine nutrition in thyroid autoimmunity is not clear. Considerable work remains to clarify the exact quantity and duration of iodine ingestion that might induce AIT. Available evidence at the most indicates an association and no causal relationship have been established.

Conclusions In any child presenting with goiter complete work up is necessary, so as to decide upon a rational treatment. A possible link between increased iodine intake and autoimmune thyroiditis was found in the study population. Excessive iodine intake may trigger thyroid auto immunity and eventually thyroid hypo function in susceptible individuals .More than adequate iodine supplementation in a region, in which iodine intake was previously mildly deficient may exacerbate the development of subclinical hypothyroidism. Supplementation programs should be tailored to a particular region and proper monitoring of the salt iodisation program is essential to achieve acceptable iodine status.

Limitations:

Not a community based survey

Absence of preiodisation data does not permit the conclusion that high value of iodine in AIT is due to salt iodisation

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