Original Articles

Juvenile Hyperthyroidism: An Experience

S. Bhadada, A. Bhansali, P. Velayutham and S.R.Masoodi

From the Department of Endocrinology, Postgraduate Institute of Medical Education and Research, Chandigarh 160 012. India.

Correspondence to: Dr. Anil Bhansali, Department of Endocrinology, PGIMER, Chandigarh 160 012. E-mail: anilbhansali_endocrine@rediffmail.com

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Objectives: *To analyze the clinical profile of juvenile hyperthyroidism at presentation, their treatment outcome; predictors of remission and relapse.* ***Methods:*** *Retrospective analysis of medical records of 56 patients with juvenile hyperthyroidism seen over a period of 16 years. A cohort of 38 females and 18 males with mean (± SD) age of 14.9 ± 3.4 years (range 3 to 18 years) was analyzed.* ***Results:*** *Majority of patients was in the age group of 12-16 years. Common symptoms observed at presentation were weight loss (82.1%), excessive sweating (78.6%), heat intolerance (76.8%), increased appetite (73.2%) and diarrhea in 48.2%. In addition, accelerated linear growth was observed in 7.1% of patients. Goiter was present in 98.2% of children; 94.5% of which was diffuse and 4.8% was multinodular. The mean ((SD) T_3 was 4.8 ± 3.4 ng/mL (N, 0.6-1.6), T_4 was 218 ± 98 ng/mL (N, 60-155) and TSH was 0.44 ± 0.36 (N, 0.5-5.5 µIU/mL). TMA positivity seen in 36.9% of patients. All patients were treated with carbimazole; subsequently 4 patients required thyroidectomy and one required radioactive iodine ablation. Mean (±SD) duration of follow-up in our patients was 4.9 ± 3 years, ranging between 1.6 to 16 years and mean (± SD) duration of treatment was 34.4 ± 22.6 months (range 12 to 120 months). Mean (±SD) duration to achieve euthyroidism was 5.2 ± 4.7 months, ranging between 1-33 months. On intention to treat analysis, remission with carbimazole was achieved in 47.6%, remaining patients failed to achieve remission with drug treatment.* ***Conclusion:*** *Graves' disease is the commonest cause of juvenile hyperthyroidism. Carbimazole is safe, effective, cheap, and easily available form of therapy. It is occasionally associated with serious side effects but requires prolonged follow up.*

Key words: *Graves' disease, Hyperthyroidism, Remission, Relapse*

HYPERTHYROIDISM in childhood and adolescence is less common compared to adult population(1). Graves' disease (GD) is the most common cause of hyperthyroidism in children as well as in adults and accounts for 10-15% of all childhood thyroid diseases(2). Hashimoto's disease is quite common in adolescents and sometimes can cause transient hyperthyroidism, which can be confused with GD. Other less common causes of hyperthyroidism in children and adolescents include benign toxic adenoma, thyroid stimulating hormone (TSH) secreting pituitary adenoma or rarely pituitary resistance to thyroid hormones and McCune-Albright syndrome(2,3).

The clinical profile of hyperthyroidism varies with age. Children have certain symptoms and signs, like hyperkinetism, accelerated linear growth, poor scholastic

performance, and weight gain, which are uncommon in adults(4). The diagnosis of hyperthyroidism is easily confirmed by thyroid function tests and radioactive iodine uptake if required. Treatment modalities for hyperthyroidism in adults include long-term anti thyroid drugs, ablative therapy including surgery and radioiodine. However, the treatment of hyperthyroidism in children is controversial, and all treatment modalities are associated with potential complications(5). The objective of the present study was to analyze the clinical profile of juvenile hyperthyroidism at presentation, treatment outcome; predictors of remission and relapse.

Subjects and methods

In this retrospective analysis, data of 84 patients were retrieved from the records of Thyroid Clinic at Nehru Hospital, Post Graduate Institute of Medical Education and Research, Chandigarh, North India, from 1986 to 2002. Inclusion criteria were age less than 18 years at presentation and duration of follow up of at least 12 months after achieving a maintenance dose for a period of at least one year. The diagnosis of hyperthyroidism was made on the basis of clinical criteria and confirmed by elevated serum T_3 (N, 0.6-1.6 ng/mL) and/or T_4 (N, 60-155 ng/mL) and suppressed TSH (<0.5 (IU/mL). The diagnosis of Graves' disease (GD) was based on diffuse goiter with increased radioactive iodine uptake. Thyroid hormone profile was performed by radioimmunoassay (RIA). Radioactive iodine uptake (RAIU) study was performed at 24 hrs (N, 15-25%) and thyroid microsomal antibody (TMA) was estimated by immunofluorescence technique. Fine needle aspiration cytology (FNAC) was also performed in some of these patients. Bone age was estimated by Greulich's and Pyle's chart(6). Patients treated with block replacement therapy and patients with follow up of less than 12 months were excluded from the study. Therapy with carbimazole was initiated with a dose of 0.6 to 0.8 mg/Kg body weight and continued till euthyroidism was achieved. The dose was titrated at 3 monthly intervals and a maintenance dose (5 mg) was continued for 12 months. We defined remission as clinical and biochemical euthyroidism for at least 1 year after antithyroid drug withdrawal and relapse as recurrence of symptoms within one year after stopping the drug(7,8). During follow up, time to achieve euthyroidism, total duration of follow up, number of relapses, complications of medical therapy, radioiodine and surgery were recorded. Out of 84 patients, fifty-six patients met the inclusion criteria and included in the study.

Statistical Analysis

The SPSS package version 10.1, 1999 (SPSS Inc Chicago, IL) was used for data analysis. Data are expressed as Mean ± SD or as percentages and P value of <0.05 was considered as significant. Chi square test was used for comparing categorical variables and non-parametric tests (Mann Whitney test) used for comparing continuous variables. Spearman's R coefficient was used for the correlation analysis between the parameters determined in the study. Regression analysis was used to determine factors in frequency outcome. Intention to treat analysis was used to calculate remission rate.

Results

The details of age and sex distribution are given in *Table I*. Their age ranged from 3 to 18 years with mean (± SD) of 14.9 ± 3.4 years (Median age 16 years) and female to male ratio of 2.1:1. The symptoms and signs observed at presentation are summarized in *Table II*. Family history was recorded in all patients. A positive family history was obtained in 5 (8.9%) patients. First-degree relatives were

TABLE I–*Age and Sex Distribution of Children with Hyperthyroidism.*

Age group	Male	Female	Total
<5	0	1	1
> 5-10	4	2	6
>10-15	6	14	20
>15	8	21	29
Total	18	38	56

involved in 3 patients (two had GD, one had hypothyroidism)

The mean (± SD) values of T_3, T_4, TSH and RAIU are given in *Table III*. Significantly high titre of TMA (1:80 dilutions) was seen in 36.9% of patients. Fine needle aspiration cytology (FNAC) was performed in 22 patients and findings were consistent with colloid goiter in 36%, lymphocytic infiltration with follicular destruction (23%) followed by fire and flare appearance (23%) and benign thyroid aspirate (18%).

All 56 patients received carbimazole in doses of 0.6 to 0.8 mg/kg body weight, in a single dose as initial treatment along with non-iodized salt. Subsequent doses were titrated at 12 weeks interval according to clinical and hormonal profile. The Mean (± SD) duration of treatment was 34.4 ± 22.6 months (range 12 to 120), duration to achieve euthyroidism was 5.2 ± 4.7 months (range 1 to 33) and duration of follow up was 4.9 ± 3.0 years (range 1.6 to 16 years). Remission was achieved in 71.4%, however on intention to treat analysis,

TABLE II–*Comparison of Symptoms and Signs in Juvenile Hyperthyroidism.*

Symptoms and signs	Present study (%)	Lafranchi, *et al*. (2) (%)	Raza, *et al*. (12) (%)
Goiter	98.2	99	98
Weight loss	82.1	54	54
Tachycardia	80.0	83	95
Excessive sweating	78.6	49	41
Tremor	78.2	61	51
Heat intolerance	76.8	33	27
Palpitation	76.8	34	–
Increased appetite	73.2	60	47
Exaggerated DTR	63.6	–	–
Eye involvement	58.9	66	71
Dyspnea on effort	60.7	–	–
Diarrhea	48.2	13	27
Menstrual disturbance	33.3	–	–
Sleep disturbance	30.4	–	22
Thyroid bruit	20.0	53	84
Murmur	10.9	–	–
Increased linear growth	7.1	–	
Proximal muscle weakness	5.4	–	
Anxiety	5.4	80	–

TABLE III–*Subjects and Parameters.*

Parameters	(Mean ± SD)
Age at presentation (years)	14.9 ± 3.4
Lag time for diagnosis (months)	7.04 ± 7.54
Duration of follow up (years)	4.9 ± 3.0
Thyroid function tests at presentation	
T_3 (ng/mL)	1.8 ± 3.4
T_4 (ng/mL)	218.5 ± 98.6
TSH (μIU/mL)	0.44 ± 0.36
Radioiodine uptake (%)	55.6 ± 19.7
Initial dose of carbimazole (mg/day)	26.3 ± 5.6
Maintenance dose of carbimazole (mg/day)	10 ± 1.7
Duration of treatment (months)	34.4 ± 22.6
Duration of achieve euthyroidism (months)	5.2 ± 4.7

remission was achieved in 40 (47.6%) patients; relapse was recorded in 5 (9%) patients. Remaining patients either lost to follow up or could not achieve euthyroidism and continued with medications. Younger ages, male sex, low heart rate at onset were associated with higher percentage of remission. However, these were not statistically significant (*Table IV*).

Four patients were subjected for subtotal thyroidectomy when they remained hyperthyroid for a period of more than 18 months despite of receiving 60 mg carbimazole daily. No surgical complication was reported in these patients except in one who developed transient hypocalcemia. Out of 56 patients, one developed agranulocytosis after three years of carbimazole therapy. Subsequently, she received ablative dose of radioiodine.

Discussion

Diffuse toxic goiter remains the most common cause of hyperthyroidism in children. The disorder is rare before the age of 3 years, increases progressively and reaches peak by adolescence(9). Onset of hyperthyroidism in majority of the children in our cohort was between 12 and 16 years of age. Although age at onset as early as 1.1 years has been reported, Mokhashi, *et al.* and others reported onset of hyperthyroidism in majority of children around 9 years of age(10,11). Hyperthyroidism is more common in female children with reported female to male ratio as high as 5:1(10). Girls to boys ratio in our study was 2.1: 1.

The weight loss, tachycardia, tremor and excessive sweating were frequently present in our patients as reported by others(2). The high incidence of symptoms and signs in our study was probably related to late presentation (delayed diagnosis). Presence of goiter was comparable in either sex; however, females had large goiter compared to males ($P < 0.05$). Exophthalmos was recorded in 30.9% of our cohort, which is comparable to other studies(11). Behavioral problems like nervousness, irritability, excessive crying and hyperactivity were reported in various other series but these were not recorded in most of our patients. However, features like thyroid acropachy, pretibial myxedema (dermopathy), thyroid storm, and periodic paralysis are rare in children and were not present in our patients.

Both autosomal recessive and dominant modes of inheritance have been postulated in genetics of hyperthyroidism. Raza et al(12) and Vadiya, *et al.*(13) have reported a positive family history in 30% and 37% of their patients respectively while only 9% of patients had the same in our study.

Thyroid hormonal profile of our patients was comparable to others(11). RAIU at 24-hours ranged from 35.9% to 75.3% in our

TABLE IV–*Remission and Patient Characteristics.*

Parameter	Remission No.	(%)	No-remission No.	(%)	P value
Age group ≤5	–		1	(100)	0.176
>5-10	6	(100)	–		0.325
>10-15	17	(73.9)	6	(26.1)	0.729
>15	17	(65.4)	9	(34.6)	0.351
Sex					
Male	15	(83.3)	3	(16.7)	0.175
Female	25	(65.8)	13	(34.2)	0.175
Heart rate					
<110 per minute	18	(90.0)	2	(10.0)	0.057
>110 per minute	22	(62.9)	13	(37.1)	0.057
BMI	16.66 ± 2.83	(73.3)	16.70 ± 3.15	(26.7)	0.962
T_3 (mean ± SD) ng/mL	4.7 ± 3.67		5.03 ± 2.09		0.790
T_4 (mean ± SD) ng/mL	210.1 ± 103.0		237.1 ± 88.8		0.384
RAIU, 24h (mean ± SD)	56.26 ± 20.19		54.08 ± 19.09		0.737

study, as compared to 41% to 86% in the series by Saxena, *et al*.(14). High RAIU at 24 hr substantiated the diagnosis of GD and excludes the possibility of subacute thyroiditis. In our cohort, 36.9% of patients had significantly high titre of thyroid microsomal antibodies (TMA). However, others reported it in 41.6% and 50% respectively(11,14). High titers of TMA in these patients represents immune mediated disease process. FNAC evidence of lymphocytic infiltration in patients with hyperthyroidism is well known(15). Vaidya, *et al*,(13) reported that 4% of patients with hyperthyroidism had evidence of thyroiditis on FNAC. In our patients it was even higher (23%), probably due to the universal salt iodination program in our country. The universal salt iodination program has been associated with increasing incidence of thyroiditis due to increased expression of major histocompatibility Class II (MHCII) antigen from thyroid follicular cells and alterations in structure of thyroglobulin, thereby becoming more antigenic. When FNAC was compared in girls and boys, lymphocytic infiltration (18% *vs*. 4.5%) and fire flare appearance (18% *vs*. 0%) were more common in girls.

We used carbimazole as the first line therapy in all patients similar to other studies (10,12). Remission with drug treatment is variable in various studies ranging from 33-64%(11,16,17), in our study it was achieved in 47.6% of patients. Girls took longer time to achieve euthyroidism and low remission rate compared to boys. This may be due to larger goiter size in girls. Among them furing follow up, 6.9% of patients developed hypothyroidism.

Children are relatively refractory to the antithyroid drugs and side side effects are more common(12). The overall incidence of side effects of drug in our series was 1.8%, which was much lower than in other pediatric series(11,17).

Block replacement therapy (BRT) using

Key Messages

- Graves' disease is most common cause of childhood hyperthyroidism.
- Carbimazole is effective, cheap, easily available and rarely associated with serious side effects; therefore we recommend it as first line therapy.

methimazole initially and later combined with L-thyroxine has been tried to achieve long term remission in patients with GD. Some studies in adults with GD have shown the beneficial effect of combination of methimazole and L-thyroxine in decreasing the incidence of recurrence, however others have refuted it(18). Raja, *et al.*(12) used BRT in juvenile hyperthyroidism and showed that it was more convenient than the titration regimen pertaining to dose adjustment and visits to hospital per year ($P < 0.001$).

The thyroid surgery and radioiodine ablation are second line treatment modalities in management of juvenile hyperthyroidism. In Europe thyroidectomy (subtotal, near total, total) is often the therapy of choice in children and adolescents with GD, after a recurrence, during or after antithyroid drug treatment (ATD), or in those who cannot tolerate ATD (2,19). Of the 56 patients in our study, only 4 patients underwent subtotal thyroidectomy and only one had transient hypocalcemia. However, Raza, *et al.*(12) more commonly documented transient hypocalcemia (59%) and vocal cord palsy (7.6%). In our patients final outcome in form of hypothroidism was comparable to others(12). Radioiodine ablation is less frequently used in Europe in contrast to those of American centers. In our series only one patient received radioiodine ablation when she developed agranulocytosis. At last follow-up after 2 years of radioiodine ablation she was remained euthyroid.

Predictors for early remission of childhood hyperthyroidism are small goiter, higher BMI, low heart rate, low radioiodine uptake and low T_3, T_4(5,20). Frequent relapses are seen in T_3-predominent GD, and those who receive either low doses or short course of anti thyroid drugs. Patients with younger age, male sex, with higher BMI, lower heart rate (<110 per minute) and relatively low T_3, T_4 levels achieved higher percentage of remission in our study, however it was not statistically significant. Other causes of delayed remission in children compared to adults may be poor compliance with drug and immunomodulatory effects of puberty.

In conclusion, Carbimazole is effective, inexpensive, cheap, easily available and rarely associated with serious side effects; therefore we recommend this as first line therapy. However, it requires frequent and prolonged follow-up. Surgery can be used as second line therapy, if hyperthyroidism is not controlled with optimum doses of carbimazole and associated with pressure symptoms. Radioiodine ablation treatment seems to be safe and effective but our experience with the same is limited.

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