Childhood Grave's-an experience from a tertiary care center

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ABSTRACT

Background: Graves' disease (GD) attributes for important cause for childhood hyperthyroidism with a prevalence of 0.02%. Initial treatment for GD is the use of antithyroid drugs (ATDs), which is well accepted. The remission rate is around about 30% of children treated with ATD. **Aims and Objective:** (1) To assess the predictors of relapse and remission after ATD in children with Grave's disease. (2) To study the clinical profile at presentation and treatment outcome of children with Grave's disease. **Materials and Methods:** We conducted a prospective cohort study of children diagnosed for GD (n = 27) and treated with either carbimazole (0.6–0.8 mg/kg), methimazole (0.2–1 mg/kg), or (propylthiouracil, 5–10 mg/kg) and continued till euthyroid state was achieved. The dose was titrated every 2 months once till the achievement of the euthyroid state. Assessment of remission and relapse was done within a year of stopping the drug. **Results:** The overall estimated relapse rate for hyperthyroidism was 54.1% (13 patients), within a year of stopping ATD with a mean duration treatment of 24.23 ± 7.44 months. Multivariate survival analysis showed that the risk of relapse (87.5%) was higher for patients of a body mass index SD score <0.5 and a large goiter. Pre-pubertal patients had higher relapse rate than pubertal patients (OR- 3.24, P = 0.04). No other clinical variables such as age, gender, and Wayne Index were significantly associated with relapse, though patients in the relapse group were younger, and had a male predominance with higher Wayne index scores. **Conclusion:** GD in children has a high relapse rate. Severity of the disease as measured by various clinical methods is important in predicting relapse.

Key words: Graves' disease; Body mass index; Antithyroid drug; Children

INTRODUCTION

Graves' disease (GD) is an autoimmune disorder which is characterized by hyperthyroidism or overactive thyroid and diffused goiter. GD attributes for important cause for childhood hyperthyroidism or thyrotoxicosis with a prevalence of 0.02%.[1] GD is the result of the complex interaction between genetic factors, environmental factors, and the immune system.[2] However, it is the most common cause for hyperthyroidism in children and adolescents.[3,4]

Current treatment strategies for patients with GD are antithyroid drugs (ATDs), radioactive iodine (RAI), and thyroid surgery. Among these, conservative as well as first-line therapy is with ATD and is everywhere well accepted. Other treatments such as thyroid surgery and RAI therapy may cause permanent hypothyroidism which may require replacement of thyroid hormone for the rest of life and oncogenic damage with RAI therapy. Due to the abovementioned reasons, most of the clinicians opt for ATD as the first line for hyperthyroidism treatment.[5,6]

The most common limitation of ATD treatment is the high relapse rate following drug withdrawal which ranges from almost 30% to 70%.[5,7,8] Prediction of remission or relapse rate among the treatment receiving hyperthyroidism cases will be very useful for the physicians treating. Several risk factors have been identified from the previous studies for predicting

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relapse after stopping ATD, for example., younger age, large size of goiters, smoking, male sex, severe biochemical disease, body mass index (BMI), and higher levels of antibodies.[5,7-9]

The aims of this prospective observational study were to assess the predictors of relapse and remission after ATD in children with Grave's disease and to study the clinical profile at presentation and treatment outcome of children with Grave's disease.

Aims and objectives
(1) To assess the predictors of relapse and remission after ATD in children with Grave's disease.
(2) To study the clinical profile at presentation and treatment outcome of children with Grave's disease.

MATERIALS AND METHODS

Study protocol: The present study was approved by the Institutional Ethics Committee of J.N.M.C Belgaum, according to their regulations. Written informed consent was obtained from all subjects before the initiation of the study.

Study design and study participants
This study was a prospective study for 5-year duration involving children with Grave's disease treated with ATD.

Inclusion criteria
Age <18 years during presentation and duration of follow-up for at least 12 months after achieving a maintenance dose for a period of at least 1 year.

Exclusion criteria
Patients with known Grave's disease who were already on ATD or those with past history of radioiodine therapy or thyroid surgery. The diagnosis of hyperthyroidism was made on the basis of clinical criteria and confirmed by elevated serum triiodothyronine (T3) (N, 1.25–2.74 nmol/L) and/or thyroxine (T4) (N, 57–159 nmol/L) and suppressed thyroid-stimulating hormone (TSH) (<0.4 mIU/L). The diagnosis of GD was based on the presence of a diffused goiter with increased uptake on Technetium-99 thyroid scan with or without eye signs. TSH, T4, T3, and thyroid peroxidase antibody (anti-TPO) were done by chemiluminescence.

Data collection
We collected information regarding the following variables at diagnosis:

Clinical features: Age, gender, family history, height, weight, pubertal status, pulse rate, goiter size, the presence of ophthalmopathy, and family history of hyperthyroidism.

Based on the signs and symptoms, Wayne Index was calculated for each patient. Ultrasonography of the thyroid was done in all cases and thyroid size was noted. We corrected for age-related differences in the volume of the normal thyroid by classification into four categories: No goiter, small (<1.5 times normal size), moderate (<1.5–2.5 times normal size), or large (<2.5 times normal size) goiter. Fine-needle aspiration cytology was performed in patients with nodularity.

To standardize the BMI for age and gender, we calculated the BMI SDS score using the World Health Organization anthropometry plus calculator.

Therapy was initiated with either carbimazole (0.6–0.8 mg/kg), methimazole (0.2–1 mg/kg), or (propylthiouracil, 5–10 mg/kg) and continued till the euthyroid state was achieved. The dose was titrated at 2 monthly intervals, and a maintenance dose was continued for at least 12 months. We defined remission as the clinical and biochemical euthyroid state for at least 1 year after ATD withdrawal and relapse or recurrence of symptoms within 1 year after stopping the drug.[1,2] During follow-up, time to achieve euthyroid state, total duration of follow-up, number of relapses, complications of medical therapy, radioiodine, and surgery were recorded.

Statistical analysis
Demographic data were expressed in percentages, and continuous data were expressed as mean ± standard deviation. Student's t-test was used for the comparison of thyroid hormone and TSH receptor levels between patients with remission and relapse state from GD after ATD treatment. Univariate and multivariate analysis was done to find the predictors for the relapse or remission of cases. All analyses were performed using Windows-based SPSS statistical package (version 20.0). The P<0.05 was significant.

RESULTS

Clinical characteristics of patients with GD:
A total of 27 patients were included in the study during our study period, among them, 22 girls and 5 boys, giving a ratio of female to male of 4.4:1. The details of age and sex distribution are given in Table 1. The age ranged from 7 to 18 years with a mean of 13.3±2.9 years, 13 patients being prepubertal and rest already in puberty. Majority of patients were in the age group of 15–18 years. There were 2 (8.33%) patients who had associated Down's syndrome.

The signs and symptoms observed at the presentation are shown in Table 2.

One patient with Down's syndrome who was on the maintenance dose of carbimazole for 2 years developed

Table 1: Age and sex distribution of children with Graves' disease

Age group	Male	Female	Total
5–10	0	4	4
10–15	3	8	11
>15	2	10	12
Total	5	22	27

Table 2: Comparison of Signs and symptoms in Childhood Graves disease

Symptoms and signs	Present study (%) (n=27)	N	Raza et al.
Goiter	100	27	98
Diffuse	92.59	25	
Nodular	7.40	2	
Weight loss	85.18	23	54
Tachycardia	92.59	24	95
Excessive sweating	81.48	22	41
Tremor	74.07	20	51
Heat intolerance	62.96	17	51
Palpitations	74.07	20	-
↑ appetite	62.96	17	471
Proptosis	70.37	19	71
Diarrhea	33.33	9	27
Menstrual disturbances	30.76	4/13	-
Sleep disturbances	25.92	7	22
Proximal myopathy	7.40	2	-
Anxiety	11.11	3	-
↓school performance	36.36	8/22	
Thyroid bruit	55.55	15	84
Murmur	7.40	2	-
Periodic paralysis	0	0	
Associated diseases Downs syndrome	7.40	2	1.7

SEX DISTRIBUTION

- ■ MALE
- ■ FEMALE

19%
81%
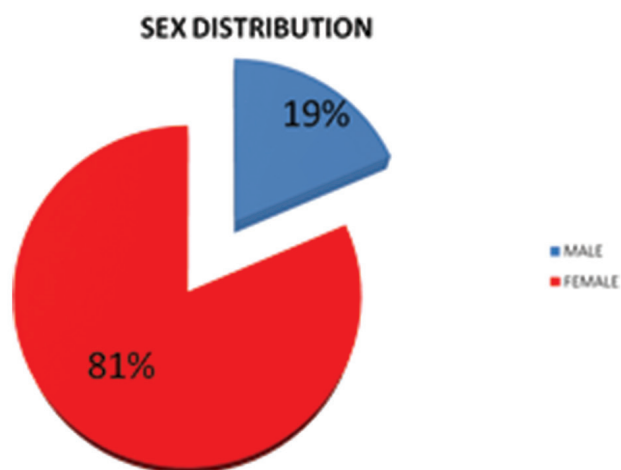
septicemia and succumbed to it. One patient did not achieve a euthyroid state with 60 mg of carbimazole and was thus subjected to thyroidectomy. One patient was lost to follow-up.

The baseline demographic information, physical examination, laboratory data, and treatment parameters of these (24) patients are shown in Table 3.

Table 3: Baseline characteristics

Variable	Mean±SD
Demographic information	
Age at presentation (years)	13.3±2.9
% Female	81.4
Family history of thyroid disease	
None	88.8
Hyperthyroid	3.7
Hypothyroid	7.4
Hyper and Hypo	0
Physical examination	
BMI (kg/m^2)	17.3±3.2
Pubertal development	
Pre-pubertal (Tanner stage 1)	48.1
Pubertal (Tanner stage 2–5)	51.8
Heart rate	116±12
Goiter	
None	0
Small	14.8
Medium	37
Large	48.1
Laboratory data	
T3 (ng/mL)	4.9±1.9
T4 (ng/mL)	264.5±83.8
T3% (% above upper range)	178.8±69.9
T4% (% above upper range)	165.3±52.3
TSH (µIU/mL)	0.22±0.1
Anti-TPO positive	77.77
Treatment parameters	
Initial dose of carbimazole (mg/day)	22.0±8.5
Maintenance dose of carbimazole (mg/day)	11.8±5.7
Duration of treatment (months)	24.1±10.1
Duration to achieve euthyroid state (months)	5±1.9

The mean duration of treatment was 24.1±10.1 months and the duration to achieve a euthyroid state was 5±1.9 months. Remission was achieved in 45.83% of patients at 1 year of follow-up. The baseline characteristics of 24 patients who fulfilled the inclusion criteria were considered for analysis for the prediction of relapse.

Predictors of relapse

Out of 24 patients who were included for analysis, 13 patients (54.1%) had relapse within a year of stopping ATD, after a mean of 24.23±7.44 months of treatment.

Univariate analysis: Patients who had a relapse, had lower BMI's and BMI SD scores, and higher heart rates at presentation.

Patients with large goiters were more likely to relapse compared with those with small or moderate goiters. Pre-pubertal children were more likely to relapse than pubertal or past pubertal children.
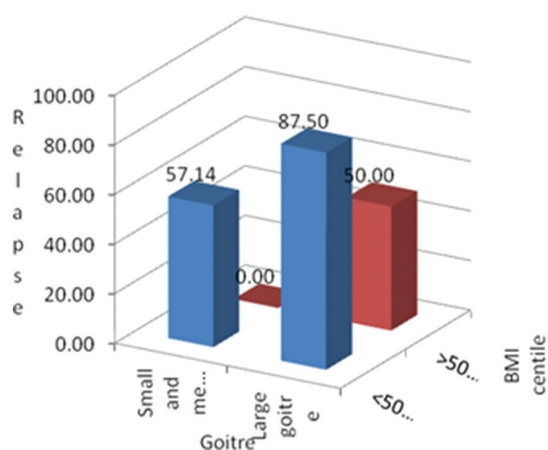
No other clinical variables such as age, gender, and Wayne Index were significantly associated with relapse, though patients in the relapse group were younger, and had a male predominance with higher Wayne index scores.

There were no significant differences between the serum T3, T4, T3% above mean, T4% above mean, TSH, and anti-TPO levels between the two groups.

The initial and maintenance dose of carbimazole, the duration of therapy, and the duration to achieve euthyroid state was not significantly different between the two groups.

Multivariate analysis

The following variables were included for regression analysis: Pubertal status, BMI SD score, heart rate, and goiter size. Among the variables entered in regression, only the BMI SD score was identified as an independent predictor of relapse. Goiter was a near predictor of relapse. Using these two variables, we classified the relapse patients into four groups using a BMI SD score of −0.5 SD and the presence or absence of goiter.

Patients with a BMI SD score <0.5 SD and a large goiter had 87.5% of relapse while patients with a BMI SD score >0.5 SD and a small/moderate goiter had a 0% relapse rate. Patients within the other two groups had an intermediate relapse rate of 50–57.14% which was the same as the study population.

DISCUSSION

GD is rare before the age of 3 years and increases progressively with age thereafter. In the present study, our data showed a similar trend, there was an increased prevalence during the pubertal years. Hyperthyroidism is more common in female children with reported female-to-male ratio as high as 5:1.[10,11] Female-to-male ratio in our study was 4.4:1. The most frequent symptoms and signs at diagnosis were goiter and tachycardia that is similar to other studies.[10-12] Weight loss, tremor, and excessive sweating were the complaints present in our patients and is very much

Table 4: Correlation analysis of all parameters of the disease with the outcome								
Parameters	**Remission (n=11)**		**Relapse (n=13)**		**OR**[a]	**T statistic**	**P**	**95% CI**	
	Mean/No. (%)	**SD**	**Mean/No. (%)**	**SD**				**Lower**	**Upper**
Age	14.32	2.55	11.96	2.85		2.11	0.05[b]	0.04	4.67
Sex									
Male	1 (20.0)		4 (80.0)				0.19[c]		
Female	10 (52.6)		9 (47.4)		1.31E-17				
Puberty									
Pre-pube	3 (25.0)		9 (75.0)		3.24E+16		0.04[c]		
Pube	8 (66.7)		4 (33.3)						
BMI	19.95	2.95	15.13	2.05		4.70	0.00[b]	2.69	6.95
BMI SD	−0.03	1.32	−0.86	1.42	3.21	3.83	0.03		
<5 percentile	1 (16.7)		5 (83.3)		7.73E+16		0.042[c]		
5–50 percentile	3 (33.3)		6 (66.7)		7.63E+16				
50–95 percentile	6 (75.0)		2 (25.0)		2.38E+00				
>95 percentile	1 (100.0)		0 (00.0)						
Goiter									
Small and medium	8 (66.7)		4 (33.3)				0.04[c]		
Large	3 (25.0)		9 (75.0)		3.31E+08				
Wayne Index	31	0.65	33	1.24		−3.45	0.23		
Pulse rate	106.36	10.50	123.85	10.50		−4.06	0.00[b]	−26.40	−8.56
T4	238.80	67.72	296.02	94.08		−1.68	0.11[b]	−127.86	13.41
T4 Percentage	149.25	42.32	185.02	58.80		−1.68	0.11[b]	−79.92	8.38
T3	4.08	1.59	5.64	1.98		−2.10	0.05[b]	−3.10	−0.02
T3 Percentage	148.91	58.19	205.95	72.19		−2.10	0.05[b]	−113.29	−0.81
TSH	0.20	0.09	0.19	0.11		0.22	0.83[b]	−0.07	0.09
TPO									
Negative	2 (40.0)		3 (60.0)				0.77[c]		
Positive	9 (47.4)		10 (52.6)		0.00E+00				
Duration of therapy	22.73	6.21	24.23	7.44		−0.53	0.60[b]	−7.37	4.37
Initial Dose	20.45	7.89	23.85	9.16		−0.96	0.35[b]	−10.71	3.92
Maintenance Dose	10.45	4.72	12.69	6.33		−0.97	0.34[b]	−7.04	2.57
Duration to Eu	4.55	2.02	5.38	1.89		−1.05	0.31[b]	−2.50	0.82

similar to other studies.[12,13] Exophthalmos was recorded in 70.3% of our cohort, which is comparable to other studies.

Till today, there is controversy regarding the best method of treatment for thyrotoxicosis in children. The three most common methods are ATD, thyroidectomy, and radioiodide therapy. All these three methods have distinct advantages and disadvantages. However, ATDs have been used as the first-line treatment in children. The duration of treatment with ATD from various studies was different ranging from 1 year to as long as 10.9 years, with a remission rate of 25–53%.[9,14] In the present study, the remission rate was 45%.

Using univariate analysis, we found that BMI, pubertal status, pulse rate, and goiter size had a prognostic value for predicting relapse. These findings indicate that the severity of the disease at diagnosis is an important determinant of the likelihood of early remission. While previous studies[9,13-15] have also implicated serum T3, T4, and the time required for T3 and T4 to normalize to be of prognostic significance, this was not found in our report.

Using multivariate analysis, we found the BMI SD score to be an independent predictor of relapse. Previous studies had variable results in assessing for the prediction of relapse and were mainly done on adults. Various studies[9,14,15] have found the initial T3 and T4 to be of prognostic significance, but these findings were not similar in other studies. The most consistent results have been regarding the goiter size with many studies supporting the contention that large goiter is a poor prognostic sign and is a predictor of relapse.[5,9,15]

Children with hyperthyroidism were studied less extensively for predictors of relapse than adults. Several studies reported that initial goiter size was helpful in predicting relapse. In our study, though large goiter was seen more commonly in the relapse group, it was not an independent predictor of relapse. Similarly, Singhal et al.,[16] did not find a significant correlation between goiter size and ability to achieve remission.

Many other studies reported a higher remission rate, like one done by Ishtiaq et al., reported remission rate of 41.9%,[17] and 43.3% by Vitti et al.,[18] 61% by Anagnostis et al.[19]

The difference between our study and the numerous studies is attributed to a number of factors such as sample size, questionnaire (investigation variables), treatment duration, and fixing the outcome variable.

The present study has some limitations. First, we undertook in a relatively smaller sample size compared to previous studies and a follow-up was limited in the study population.

Patients who were euthyroid for a year after stopping medications were considered to have achieved remission. Because many patients were lost to follow-up thereafter we cannot exclude the possibility of late relapse in them. We could not study certain variables that are of theoretical interest such as the TRAbs.

Limitations of the study

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CONCLUSION

GD in children has a high relapse rate. Severity of the disease as measured by various clinical methods is important in predicting relapse. BMI SD score is an independent predictor of relapse. BMI SD score and goiter size can be used to stratify patients according to the probability of relapse and provide useful information for counseling patients and therapeutic decision-making.

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