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Clinical features and predictors of remission in children under the age of 7 years with Graves' disease

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ABSTRACT

Importance: Graves' disease (GD) is rare in children under the age of 7 years. Children with this disease exhibit greater thyrotoxicity at diagnosis and require a longer course of medical therapy, compared with pubertal and postpubertal children and adults.

Objective: To investigate the clinical features and identify predictors of remission in children under the age of 7 years with GD.

Methods: This retrospective study included 77 children who were diagnosed with GD under the age of 7 years and were treated in the Department of Endocrinology, Beijing Children's Hospital from 2010 to 2018. Clinical manifestations, laboratory data, and follow-up records were collected for all patients. Children who achieved remission of treatment with methimazole were compared with those who had persistent disease to identify which variables were associated with remission; multiple logistic regression and Cox regression analyses were used to evaluate interactions among predictive variables.

Results: Sixty-three boys and 14 girls were included; the median age at diagnosis was 4.2 years (interquartile range: 3.2–5.3 years). Forty-six (56.7%) patients had no family history of thyroid disease, 17 patients had family history of thyroid disease and 14 patients with unknown family history. Of the 77 patients, 18 (23.4%) patients achieved remission of treatment with methimazole and 59 patients did not; moreover, 51 (66.2%) had Graves' ophthalmopathy. Univariate analyses revealed no significant differences between the remission group and non-remission group in terms of age at diagnosis, sex, initial goiter size, or initial thyroid hormone concentration. However, there were a trend of correlation between the initial level of thyroid peroxidase antibody (TPOAb) and remission status (univariate analysis *OR* 1.002, $P = 0.038$; multivariate analysis *OR* 1.004, $P = 0.019$). Similar results were observed in univariate analysis of the initial thyrotropin receptor antibody (TRAb) level, but this association was not significant in multivariate analysis. Cox regression analyses revealed that children with high TRAb level required longer duration of remission, compared with low TRAb level (*OR* 0.950, 95% *CI* 0.904–0.997, $P = 0.037$).

Interpretation: Initial TRAb level was an independent predictor of remission outcome in young children under the age of 7 years with GD. Initial TRAb level may predict the likelihood of remission in patients with young-age-of-onset GD.

KEYWORDS
Graves' Disease, Children, Remission

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INTRODUCTION

Graves' disease (GD) is rare in children and adolescents, with a frequency of 0.1–3.0 per 100 000.[1] However, because of the low prevalence in prepubertal children, clinical studies tend to include younger children within the larger group of adolescents; thus, these children are not analyzed separately.[2-5] To the best of our knowledge, the clinical characteristics of Chinese children under the age of 7 years with GD have not yet been reported.

The diagnosis of GD is more complicated in younger patients than in adults. Classic symptoms of GD include heat intolerance, increased appetite, weight loss, protruding eyes, palpitations, inattentiveness, and school problems. Characteristic physical findings include tachycardia, widened pulse pressure, goiter, fine tremor, and hyperreflexia.[1]

The treatment options for children with GD include antithyroid drugs (ATDs), thyroidectomy, and radioactive iodine therapy. ATDs therapy is the first-line treatment for children with GD. The American Thyroid Association and the American Association of Clinical Endocrinologists recently strongly recommended that methimazole (MMI) should be used to treat GD in children,[6] because propylthiouracil (PTU) sometimes causes severe adverse events (e.g., liver failure and antineutrophil cytoplasmic antibody-associated vasculitis).[7] Unfortunately, the GD remission rate following treatment with ATDs, is reportedly lower in children than in adults.[8,9] In previous studies of children who were treated with antithyroid medication, 25% achieved remission within 2 years of starting treatment.[2,4]

Therefore, this retrospective study investigated the clinical features and aimed to identify influencing factors of remission in children under the age of 7 years with GD.

METHODS

Ethical approval

This study was approved by the Ethical Committee of Beijing Children's Hospital. Written formed consent was waived because the data analysis was performed anonymously in this retrospective study.

Participants

The patients who were newly diagnosed with GD under the age of 7 years and was treated in the Department of Endocrinology, Beijing Children's Hospital from 2010 to 2018 were included in this study. The diagnostic criteria for GD are included in the American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis (2016). Overt hyperthyroidism is defined as a subnormal (usually undetectable) serum thyrotropin (TSH) level, with elevated serum levels of triiodothyronine (T3) and/or estimated free thyroxine (FT4). Assessment of thyrotoxic manifestations includes goiter size, obstructive symptoms, severity of Graves' orbitopathy, and level of TSH receptor antibody (TRAb). Patients with hyperthyroidism caused by medications, thyroid adenoma, hyperthyroid phase of Hashimoto's thyroiditis, and neonatal hyperthyroidism were excluded.[10]

All patients were initially treated with MMI. The initial dose of MMI was 0.5–1.0 mg/kg per day (up to a limit of 30 mg/d) and the dosage was adjusted at intervals of approximately 6–8 weeks. MMI treatment was discontinued when a patient's TRAb level was within the normal range. Remission was defined as maintenance of euthyroidism for more than 12 months after discontinuation of ATDs treatment and the absence of any relapses during the follow-up period.[11]

All patients underwent extensive baseline physical and laboratory examinations. The following parameters from medical records were collected, including outpatient follow-up time, sex, age at diagnosis, body height and body weight, family history of autoimmune thyroid disease clinical diagnosis of Graves' ophthalmopathy, goiter size at diagnosis, TSH, serum levels of total triiodothyronine (TT3), free triiodothyronine (FT3), total thyroxine (TT4), FT4, TRAb, and thyroid peroxidase antibody (TPOAb), ATDs-associated adverse events (e.g., rash, arthritis, liver function, neutropenia) and duration of ATDs treatment.

Serum thyroid hormone concentrations and thyroid antibody levels were measured at the laboratory within Beijing Children's Hospital. Reference values were as follows: TT3 1.08–3.23 nmol/L; FT3 3.30–8.25 pmol/L; TT4 51.48–154.45 nmol/L; FT4 8.37–29.60 pmol/L; TSH 0.4–4.0 mIU/L; TPOAb < 34 IU/mL; and TRAb <1.75 IU/mL.

Statistical analysis

Quantitative variables are shown as by mean ± SD; those that did not exhibit normal distributions are shown as median (IQR). Qualitative variables are shown as *n* (%). Univariate and multivariate logistic regression analyses were used to identify influencing actors associated with remission. Cox univariate and multivariate regression analyses were used to identify influencing factors associated with remission duration.

Variables with $P < 0.1$ in univariate analysis were included in multivariate analysis. Cox proportional hazards models were used to analyze correlations between clinical factors and prognosis. The results are shown as hazard ratio (*HR*) and 95% confidence interval (95% *CI*). All statistical tests were two-tailed, and *P* values less than 0.05 were considered statistically significant. SPSS Statistics, version 22.0 was used for all statistical analyses.

TABLE 1 Demographic and clinical characteristics of patients with Graves' disease

Items	Remission group (n = 18)	Non-remission group (n = 59)	P
Age at diagnosis (years)	4.4 (3.8–5.3)	3.9 (3.1–5.4)	0.373
Gender			0.499
Male	2 (11.1)	12 (20.3)	
Female	16 (88.9)	47 (79.7)	
Family History of thyroid disease			1.000
Missing	1 (5.5)	13 (22.0)	
No family history	12 (66.7)	34 (57.6)	
First degree relatives	3 (16.7)	7 (11.9)	
Second degree relatives	2 (11.1)	5 (8.5)	
Initial goiter size			0.469
Missing	1 (5.6)	2 (3.4)	
Normal	3 (16.7)	6 (10.2)	
I	3 (16.7)	6 (10.2)	
II	10 (55.5)	45 (76.3)	
III	1 (5.6)	0	
Graves' ophthalmopathy	11 (61.1)	40 (67.8)	1.000
Initial TT_3 (nmol/L)	4.13 (3.80–6.91)	5.73 (4.03–8.50)	0.270
Initial TT_4 (nmol/L)	255.71 (206.64–321.88)	269.49 (204.75–325.85)	0.891
Initial FT_3 (pmol/L)	17.41 (12.22–28.29)	28.42 (19.70–37.90)	0.094
Initial FT_4 (pmol/L)	47.02 (41.61–58.40)	61.7 (43.13–68.88)	0.038*
Initial TPOAb (IU/mL)	1000.00 (526.00–1000.00)	188.05 (43.30–840.00)	0.104
Initial TRAb (IU/mL)	21.70 (8.23–36.72)	36.27 (22.47–40.00)	0.050
Initial MMI dose ($mg \cdot kg^{-1} \cdot d^{-1}$)	0.81 (0.71–0.92)	0.83 (0.63–0.97)	0.979

Data was shown as n (%) or median (interquartile range). *$P < 0.05$. TT3, total triiodothyronine; TT4, total thyroxine; FT3, free triiodothyronine; FT4, free thyroxine; TPOAb, thyroid peroxidase antibody; TRAb, thyrotropin receptor antibody; MMI, methimazole.

RESULTS

General information

This retrospective study reviewed the medical records of 77 children. The median age at GD onset was 4.2 years (IQR: 3.2–5.3 years). Sixty-three (81.8%) girls and 14 (18.2%) boys were included; these patients were divided into two groups based on the criteria described in the Methods section. Eighteen patients in the remission group and 59 patients in the non-remission group. Clinical characteristics and laboratory data of the two groups are shown in Table 1. No differences were found in age, sex, family history, initial goiter size, and initial TT3, TT4, FT3, TPOAb level, and MMI dose between the groups. Eleven patients in remission group and 40 patients in non-remission group had Graves' ophthalmopathy, but no statistical significance between the two groups.

MMI-induced adverse events

All patients were initially treated with MMI. The median MMI treatment time was 2.6 years (1.4–3.8 years). The median treatment period among patients who achieved remission was 2.9 years (2.3–4.3 years).

Adverse events were encountered in 29 patients during MMI treatment. No patients experienced fatal adverse events. The most common adverse events were leukopenia, neutropenia, and liver dysfunction. The main type of liver dysfunction was an elevated ALT level. Seventeen patients developed neutropenia; after treatment with glucuronolactone and leucogen, their biochemical indexes and white blood cell counts returned to normal.

Influencing factors associated with remission

In this study, 18 patients (23.4%) achieved remission. Univariate analyses revealed no significant differences in age at diagnosis, sex, initial goiter size, or initial thyroid hormone concentration. However, there were a trend of correlation between the initial level of TPOAb and remission status (univariate analysis OR 1.002, $P = 0.038$; multivariate analysis OR 1.004, $P = 0.019$). Similar results were observed in univariate analysis of the TRAb level, but this association was not significant in multivariate analysis (Table 2).

Then duration of remission was included in the univariate and multivariate Cox regression analysis. The result

TABLE 2 Univariate and multivariate logistic regression analyses of factors associated with remission in children with Graves' disease

Variables	Univariate			Multivariate		
	OR	95% *CI*	*P*	*OR*	95% *CI*	*P*
Age at diagnosis (years)	1.137	0.750–1.723	0.545			
Sex	0.490	0.099–2.427	0.382			
Initial goiter size						
Normal *vs.* II	2.045	0.441–9.491	0.361			
I *vs.* II	2.045	0.441–9.491	0.361			
Initial TT3 (nmol/L)	0.998	0.994–1.002	0.278			
Initial TT4 (nmol/L)	0.989	0.946–1.033	0.606			
Initial FT3 (pmol/L)	0.955	0.904–1.008	0.093	0.990	0.910–1.077	0.810
Initial FT4 (pmol/L)	0.980	0.950–1.010	0.186			
Initial TPOAb (IU/mL)	1.002	1.000–1.004	0.038*	1.004	1.001–1.007	0.019*
Initial TRAb (IU/mL)	0.945	0.894–0.998	0.044*	0.928	0.857–1.005	0.064
Initial MMI dose ($mg \cdot kg^{-1} \cdot d^{-1}$)	1.043	0.072–15.201	0.975			

*$P < 0.05$. *OR*, odds ratio; *CI*, confidence interval; TT3, total triiodothyronine; TT4, total thyroxine; FT3, free triiodothyronine; FT4, free thyroxine; TPOAb, thyroid peroxidase antibody; TRAb, thyrotropin receptor antibody; MMI, methimazole.

showed that children with high TRAb level required longer duration of remission, compared with low TRAb level (*HR* 0.950, 95% *CI* 0.904–0.997, $P = 0.037$). This result revealed that the initial TRAb level was an independent predictor of remission outcome in children under the age of 7 years with GD.

DISCUSSION

Hyperthyroidism is much rarer in children than in adults, such that diagnoses in children constitute approximately 1%–5% of diagnoses in all age groups.[12] Increased incidences of autoimmune diseases, including type 1 diabetes mellitus and celiac disease, have been reported in children and adolescents in recent years; a similar increase has been suggested for hyperthyroidism.[13-15] GD is the most common cause of hyperthyroidism in children. GD is common in girls, with peak in prevalence during adolescence. Young-age-of-onset GD differs from adolescent hyperthyroidism. Lazar et al[1] studied Graves' thyrotoxicosis in seven prepubertal children (6.4 ± 2.4 years), compared with 21 pubertal children (12.5 ± 1.1 years) and 12 postpubertal children (16.2 ± 0.8 years). In the prepubertal group the main complaints were weight loss and frequent bowel movements (86%), whereas typical symptoms (irritability, palpitations, heat intolerance, and neck lump) occurred significantly less often.[1] These symptoms and signs may have been present, but were overlooked or misinterpreted by the patients' parents. Prepubertal children with GD reportedly exhibit greater thyrotoxicity at diagnosis and require a longer course of medical therapy, compared with pubertal and postpubertal children and adolescents.[16]

As noted in the Introduction, treatment options for children with GD include antithroid drugs, radioactive iodine ablation and thyroidectomy. Antithroid drugs are often preferred for initial treatment.[17] MMI is strongly recommended for treatment of children with GD. The frequency of adverse reactions to MMI is reportedly 1%–30%.[18] In our study, no serious adverse events were observed, such as agranulocytosis or severe liver failure. In total, 29 minor adverse effects were observed, including leukopenia, neutropenia, and slightly elevated transaminase levels. These adverse reactions were not serious and the patients who have side effects recovered after reduction of MMI dosage.

TABLE 3 Cox regression analyses of factors associated with duration of remission in children with Graves' disease

Variables	Univariate		
	HR	95% *CI*	*P*
Age at diagnosis (years)	1.004	0.703–1.433	0.984
Sex	0.441	0.099–1.972	0.284
Initial goiter size			
Normal *vs.* II	2.565	0.691–9.514	0.159
I *vs.* II	2.989	0.800–11.171	0.104
Initial TT3 (nmol/L)	0.999	0.996–1.003	0.690
Initial TT4 (nmol/L)	0.985	0.944–1.029	0.500
Initial FT3 (pmol/L)	0.988	0.940–1.039	0.651
Initial FT4 (pmol/L)	0.993	0.965–1.022	0.631
Initial TPOAb (IU/mL)	1.001	1.000–1.003	0.154
Initial TRAb (IU/mL)	0.950	0.904–0.997	0.037*
Initial MMI dose ($mg \cdot kg^{-1} \cdot d^{-1}$)	0.390	0.028–5.468	0.484

*$P < 0.05$. *HR*, hazard ratio; *CI*, confidence interval; TT3, total triiodothyronine; TT4, total thyroxine; FT3, free triiodothyronine; FT4, free thyroxine; TPOAb, thyroid peroxidase antibody; TRAb, thyrotropin receptor antibody; MMI, methimazole.

The difficulty in treatment of hyperthyroidism in children lies in the remission and relapse. Although remission occurs in 40%–60% of adults,[19,20] it is less common in prepubertal and pubertal children, in whom remission occurs at rates of 20%–30% and 15%, respectively.[16,21-24] Fewer than 25% of patients achieve remission within 2 years of beginning antithroid drugs therapy. In this study of 77 children under the age of 7 years with GD, 23.4% achieved remission. Our results are similar to the findings in previous studies.

To the best of our knowledge, there have only been a few studies regarding prognostic factors in children and adolescents with Graves' disease; although a number of variables have been investigated to determine whether they influence the risk of relapse, the results remain inconclusive.[1,2,25] In prior studies, older age, greater body mass index (BMI) at diagnosis, smaller goiter size, greater initial dosage, and prolonged drug treatment were correlated with a greater likelihood of remission.[4,25]

Our results confirmed that the initial TRAb level is an independent predictor of remission outcome in children under the age of 7 years with GD. This indicator may predict the likelihood of remission in patients with young-age-of-onset GD. Similar results were found in the study of hyperthyroidism children regardless of age.[23,24] But another study have suggested that the TRAb cannot be used as a predictor of remission. Glaser et al[26] studied 51 children who had Graves' disease and compared children who achieved remission after 2 years with those who had persistent disease to determine which variables were associated with remission. They founded that there were no significant differences in the frequency of positive thyroid antibody tests between the remission group and the non-remission group.[26] Some scholars argue that current data do not support the use of TRAb determination in predicting the outcome of Graves' disease because there is significant variability in published data with respect to assay methodology, population characteristics, and study design. TRAb may have both stimulatory and inhibitory effects; current TRAb assays lack specificity and may yield positive results for patients with other thyroid diseases.[27] However, it should be noted that these subjects were not grouped by age. Therefore, the role of TRAb in the remission of hyperthyroidism children in different age groups needs further study.

The selection of ideal treatment for children under the age of 7 years with GD is often problematic; doctors and patients must consider the risks and benefits of each treatment option. The predictors identified in this study could help to recognize patients who are candidates for alternative therapy, such as surgery or radioiodine therapy. Importantly, this was a retrospective study. Thus, further collaborative and prospective studies are needed to confirm these data and improve the complex clinical problems of pediatric patients with Graves' disease.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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