Graves Disease in Children: Thyroid-Stimulating Hormone Receptor Antibodies as Remission Markers

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Objective To evaluate clinical and biochemical features of 115 children (98 female, mean age 11.3 ± 3.5 years) with Graves disease to identify possible determinants of remission.

Study design We defined as positive outcome the improvement of clinical features and restoration of euthyroidism or induction of hypothyroidism after antithyroid drug (ATD) therapy and as negative outcome hyperthyroidism persistent over 2 years of ATD therapy or relapsed after ATD withdrawal.

Results Thirty-eight children (33%) had remission after 2 years of ATD therapy. The absence of goiter at diagnosis was correlated with a better outcome. Median thyroid-stimulating hormone receptor antibody (TRAb) values at diagnosis were significantly lower in patients with a positive outcome ($P = .031$). We found a significant relationship between the time required for TRAb normalization and the patient outcome; TRAb normalization within 1 year from time of Graves disease diagnosis was significantly more common among patients with a positive outcome ($P < .0001$), and the mean time for TRAb normalization was significantly shorter in patients with a positive outcome (1.3 ± 0.8 years) compared with that observed in patients with a negative outcome (2.5 ± 2.7 years, $P = .026$).

Conclusions Although no clinical variable investigated is constantly associated with a definite outcome, the absence of goiter at the diagnosis may be associated with a better outcome. The most relevant predictor of Graves disease outcome was serum level; TRAb at time of Graves disease diagnosis less than 2.5 times the upper reference limit, TRAb normalization during ATD, and TRAb normalization timing each may predict positive outcomes. These results may have a role in the empiric clinical management of pediatric patients with Graves disease. *(J Pediatr 2014;164:1189-94)*.

Graves disease in childhood is a rare autoimmune disorder and accounts only for 1%-5% of all patients with Graves disease. Despite its rarity, it is the most frequent cause of hyperthyroidism in children and adolescents, causing more than 95% of cases of pediatric thyrotoxicosis.[1,2] The incidence of Graves disease in children is reported in 1 per 100 000 person/years, increasing from 0.1 per 100 000 person/years in young children to 3 per 100 000 during puberty (peak age of diagnosis 11-15 years), with a strong female-to-male predominance (5:1-10:1).[3,4] The main clinical features in children are goiter, tachycardia, nervousness, hypertension, tremor, weight loss despite increased appetite, hyperactivity, irregular menses, ophthalmopathy, heat intolerance, and diarrhea. Graves disease is caused by the activation of the thyroid-stimulating hormone (TSH) receptor by thyroid-stimulating hormone receptor antibodies (TRAbs).

Current treatment approaches include antithyroid drugs (ATDs), which are commonly used as the first-line treatment, or thyroid ablation with either radioactive iodine therapy or thyroidectomy. Management of Graves disease in childhood remains an important controversy in endocrinology because of the high rate of relapses when ATDs are used and because no single treatment modality consistently restores euthyroidism.[5-7] Although remission in adults is 40%-60%,[23,24] these rates are less common in prepubertal and pubertal children, in whom remission occurs in 20%-30% and 15%, respectively.[6,8-14]

There are only a few studies focusing on prognostic factors in children and adolescents with Graves disease,[11,13-16] and although a number of variables have been investigated to evaluate the risk of relapse, results still are inconclusive. An older age, a greater body mass index (BMI) at diagnosis, a smaller goiter size, a greater initial dosage, and prolonged drug treatment are among the factors analyzed that correlate with a greater likelihood of remission.[11,13,15-17] Therefore, children and adolescents usually undergo longer periods of drug treatment than adults, despite the absence of an evidence-based strategy for disease management.

ATD	Antithyroid drug
BMI	Body mass index
fT3	Free triiodothyronine
fT4	Free thyroxine
ROC	Receiver operating curve
TRAb	Thyroid-stimulating hormone receptor antibody
TSH	Thyroid-stimulating hormone

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We sought to analyze the clinical and biochemical features of a cohort of Italian children and adolescents with Graves disease to correlate these factors with the outcomes, and in doing so to identify possible determinants of Graves disease remission.

Methods

We retrospectively included 115 patients (98 female and 17 male; mean age at Graves disease diagnosis 11.3 ± 3.5 years, min 3.4 years, max 15.9 years) patients with Graves disease, all white, from 5 Italian pediatric endocrine departments. Ethics approval for this study was provided by the Ethics Committee of the Italian Children's Hospital.

In Italy, there is a status of mild iodine deficiency, according to the International Council for the Control of Iodine Deficiency Disorders Global Network (www.iccidd.org); the median value of urinary iodine concentration is 50-99 μg/L (normal value 100-299 μg/L); no significant differences between the 5 areas considered in our study were noted (www.iss.it/osnami/).

The diagnosis of Graves disease was based on the presence of typical clinical features and by high serum levels of free triiodothyronine (fT3) and free thyroxine (fT4), suppressed levels of TSH, and a positive titer of TRAb. We excluded patients with Down syndrome.[18] Only patients with at least 2 years of follow-up were included.

Data on family histories of thyroid autoimmune diseases in first-degree relatives, on personal histories of nonthyroid autoimmune diseases, age, sex, height, weight, BMI, Tanner pubertal stage, and clinical features of Graves disease (tachycardia, weight loss, tremors/hyperactivity, diarrhea, increase growth velocity, hypertension, visible goiter, ophthalmopathy) were recorded. Hypertension is defined as average systolic blood pressure and/or diastolic blood pressure that is greater than or equal to the 95th percentile for sex, age, and height on 3 or more occasions, in according to The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (2005)[19]; goiter was evaluated as visible or not visible at clinical evaluation.

We defined clinical severe presentation as the presence at onset of at least 2 of the following features: tachycardia, hypertension, weight loss, and/or ophthalmic abnormalities.[20] BMI (kg/m^2) was calculated as: weight (kg)/height^2 (m); to standardize for age and sex. BMI-SDS were calculated according to the LMS method.[21] Rolland-Cacherà tables[22] for BMI were used as reference.

All children were treated with methimazole at an initial daily dose of 0.5-0.7 mg/kg/day (median dose 0.50 [0.42-0.56] mg/kg/day). This dose was subsequently titrated and adjusted to maintain euthyroidism, based on the results of serum thyroid hormone testing during the follow-up. All children were treated for a period of 18-24 months. Besides thyroid function at time of Graves disease diagnosis, we also registered and studied the values of serum fT3, fT4, and TSH concentrations after 3 months of ATD therapy.

We defined as a positive outcome a Graves disease remission consistent with the improvement of clinical features and restoration of euthyroidism or induction of hypothyroidism after ATD therapy. A negative outcome was defined as hyperthyroidism persistent over 2 years of ATD therapy or relapsed after ATD withdrawal. We compared the clinical and biochemical variables studied in the positive and negative outcome groups. The second-line therapy used in patients presenting with hyperthyroidism not controlled by ATD was total/near-total thyroidectomy or radioiodine therapy.[7]

Biochemical Determinations

Free T3 and fT4 were measured by radioimmunoassay: the normal fT3 range is 1.8-4.2 pg/mL, and the normal fT4 range is 8-19 pg/mL. TSH was determined by immune radiometric assay with a normal range of 0.5-4.4 μU/mL.

The biochemical determinations of TRAbs were collected in different laboratories with the following kits: Receptor Antibody (TRAb) RIA kit (with calibrators; KRONUS, Inc, Star, Idaho) with a positive value >1.5 U/L and a negative value ≤1.0 U/L; RiaRSR TRAb Thyrotropin Receptor Autoantibody RIA Kit (RSR Limited, Cardiff, United Kingdom) with a positive value ≥15 u/L and a negative value <10 u/L; and TRAK Human Radioreceptor assay (BRAHMS Diagnostica, Berlin, Germany) for the quantitative determination of TRAbs in human serum (coated tube system; BRAHMS Diagnostica), with a positive value >1.5 IU/L and a negative value <1.0 IU/L.

Because the biochemical determinations (fT3, fT4, TSH, and TRAb) were collected in different laboratories that use different reference ranges, data were first converted in the same unit of measurement[23] and then standardized with the following formula, which takes into account different reference ranges adopted in the laboratories of the various participating centers:

$$Value_{st} = \left[\frac{(Value_{PC} - Min_{PC})}{(Max_{PC} - Min_{PC})} \times (Max_{Ref} - Min_{Ref})\right] + Min_{Ref},$$

where $Value_{st}$ = standardized value, $Value_{PC}$ = value of the participating center, Min_{PC} = minimum of the reference range of the participating center, Max_{PC} = Maximum of the reference range of the participating center, Max_{Ref} = maximum of the reference range used as "standard reference," and Min_{Ref} = minimum of the reference range used as "standard reference." For example, a value of TRAb equal to 0.75 observed in a participating center in which the adopted reference range is 0-1.5 will turn out in a standardized value of 5 if the reference range used as standard is 0-10.

Statistical Analyses

Descriptive statistics were performed, qualitative variables were summarized in terms of absolute frequencies or percentages, and quantitative variables were summarized in terms of medians with first and third quartiles or mean ± SD.

A comparison of frequencies was performed by the χ^2 test or by the Fisher exact test (in case of expected frequencies