Prediction of relapse after antithyroid drug therapy of hyperthyroidism through assessment of peak systolic velocity of superior thyroid artery

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Objective: To explore whether assessment of peak systolic velocity of superior thyroid artery can predict relapse after anti-thyroid drug therapy of hyperthyroidism. Methods: Seventy patients with hyperthyroidism were recruited and treated with antithyroid drug according to the national guideline, the thyroid and superior thyroid artery were evaluated by color Doppler ultrasound, and the blood velocity was measured and analyzed. 30 people with euthyroid were selected as control. Results: Twenty-six of 70 patients with hyperthyroidism treated with anti-thyroid drug relapse six months after remission, accounting for 37.1%. There was no significant difference between relapse patients and patients without relapse for peak systolic velocity of pretreatment. The peak systolic velocities were significant difference between remissive and relapse patients. The MV1-MV2/MV1s was significant difference between remissive and relapse patients. Area under ROC curve of peak systolic velocities of the superior thyroid arteries of remissive patients and euthyroid subjects was 0.773, the cutoff point was 40.3 cm/s, and sensitivity and specificity were 84.6% and 65.0%, respectively. Area under ROC curve of MV1-MV2/MV1s of the superior thyroid arteries of relapse patients was 0.870, the cutoff point was 0.525, and sensitivity and specificity were 86.4% and 69.2%, respectively. Conclusion: The determination of peak systolic velocity of superior thyroid artery and relevant parameters can help predict relapse after anti-thyroid drug therapy of hyperthyroidism.

1. Introduction

Pathogenesis of primary hyperthyroidism has not been elucidated completely, antithyroid drug therapy is a routine solution for hyperthyroidism, however, some patients easily relapse after drug withdrawal[1,2]. Predictive assessment whether the disease relapse after drug withdrawal has certain significance, e.g., to adjust the therapeutic regimen before drug withdrawal. Extensive research has been conducted by clinicians and professionals, but the clinical value of the research results has not yet been widely acknowledged[3-10]. The blood flow velocity of thyroid artery of patient with hyperthyroidism usually increases, which is usually in normal range in people with euthyroid. These indicate that the blood flow velocity of thyroid artery relates to the state of thyroid function. Evaluating thyroid arterial hemodynamics through color Doppler ultrasonography has been regarded as one of the reference indexes for the evaluation of curative effect of antithyroid drug therapy, but the research results are still inconsistent[2,3,11-13]. We hypothesized that dynamic analysis of changes for blood flow velocity of thyroid artery before and after treatment may provide more useful information for predicting relapse after anti-thyroid drug withdrawal. In this study, 70 patients with hyperthyroidism referring to our hospital were evaluated by color Doppler ultrasound, and the hemodynamics of superior thyroid artery were determined and analyzed at pretreatment and the end of 18 months therapy, with the aim to investigate whether the determination of peak systolic velocity of superior thyroid artery and relevant parameters can help predict relapse after antithyroid drug therapy of hyperthyroidism.

2. Materials and methods

2.1 Sample collection

Patients referred to the department of endocrinology of our hospital with suspected hyperthyroidism between September 2014 and December 2016 was considered. Patient’s age, medical history, symptoms, signs, height, weight, heart rate, blood pressure, TSH, FT3, FT4, routine tests of the blood and urine, medication, etc were
recorded. Clinical manifestations of the patients were documented, including varying degrees of palpitations, heat intolerance, increased perspiration, nervousness, irritability, excessive appetite, weight loss, hand tremors, and so on. In follow-ups, the above items were noted and compared, and adverse drug reaction was focused. Seventy female patients with hyperthyroidism were enrolled in final, with the age of 18-45 years old (mean 62 years old). All patients were treated with antithyroid drug (methimazole, propylthiouracil, methylthiouracil, etc.) according to the national guidelines. Thirty people with euthyroid was selected from our hospital’s staff who undergo routine health screen and patients with suspicious hyperthyroidism (afterwards laboratory tests showed no abnormal) as control, with age of 20-43 years old (mean 35 years old).

2.2 Inclusion criteria and exclusion criteria

The inclusion criteria were that female patients with hyperthyroidism and involving no item in the exclusion criteria. The diagnostic criteria of hyperthyroidism included: (1) Presence of symptoms and signs of high metabolism; (2) Diffusely thyroid enlargement; (3) Elevated level of free triiodothyronine (FT3) and free thyroxine (FT4); decreased level of thyroid stimulating hormone (TSH). The exclusion criteria were: Graves’ disease with infiltrating exophthalmos, nodular toxic goiter, thyroid adenoma with autonomous hyperthyroidism, anatomical variation of the thyroid gland, secondary hyperthyroidism caused by other causes, tuberculosis, pregnancy and breast feeding, and other serious diseases such as SLE, hypertension, diabetes, anemia, atrial fibrillation, premature beats, conduction block, heart failure, myocardiopathy, renal failure, liver cirrhosis, rheumatoid arthritis, congenital heart diseases, giving up treatment due to adverse drug reactions, medication of 4 to 6 weeks without remission, dropping out of treatment due to other reasons, poor treatment compliance. Non-remission hyperthyroidism refers to those who show on significant improvement in clinical symptoms, signs, and/or laboratory tests for at least 18 months treatment or relapse 6 months after remission and drug withdrawal. Remission hyperthyroidism refers to those who have significant improvement in clinical symptoms, signs, and/or laboratory tests for at least 18 months treatment or not relapse 6 months after remission and drug withdrawal.

2.3 Thyroxine and thyrotropin releasing hormone examination

FT3, FT4, and TSH, with normal reference range of 2.63-5.70 pmol/L, 9.01-19.05 pmol/L, and 0.35-4.94 mIU/L, respectively, were determined using Abbott I2000SR (Automatic Chemiluminescence Immunoanalyzer, Illinois, USA).

2.4 Color Doppler ultrasonography evaluation

Siemens Acuson S 2000 (Siemens Medical Solutions, Inc, Malvern, PA, USA) with a linear transducer with frequency 6.0-14.0 MHz was used for the study of the thyroid and thyroid arteries. Color Doppler ultrasonography was performed by the same physician at pretreatment, after 6 weeks of treatment and after 12 months of treatment. The examinee lay supine on table, padded the neck with a soft pillow, with the head retroversion, and fully exposure of the ventral neck. Two-dimensional ultrasound imaging was performed to examine the thyroid gland and lymph nodes of the neck, then hemodynamic evaluation was performed on the superior thyroid artery (STA). STA was detected with the probe placed lightly on the right and left thyroid upper pole, after the STA was showed on color Doppler flow imaging, the color gain was adjusted to appropriate condition, the gate of pulsed Doppler sampling was placed at the center of the target blood vessel. The sampling volume was set as 2 mm. The angle between the sound beam and the vascular blood flow was set to 60° (as shown on Figure1 and 2). Pulse Doppler was used to measure the (maximal) peak systolic velocity (MV), end-diastolic velocity (EV) of STA, and the blood flow resistance index was calculated automatically. The mean MV, EV, and RI of the bilateral arteries were calculated. The blood velocity of STA of patients in control group was measured once and in the hyperthyroidism patients was measured two or three times at pretreatment and the end of therapy, respectively. Data of each group were analyzed at the end of the follow-ups.

Methods to calculate the relative changes of blood flow velocity of STA: The mean value of the peak velocity of STA on both sides at the initial diagnosis (MV1) subtracted the mean value of the peak velocity of STA on both sides at the end of regimen of drug therapy (MV2), the gain of MV1 minus MV2 was divided by MV1, and the result was the decrease rate of blood flow velocity after treatment (MV1-MV2/MV1).

2.5 Statistical analysis

Statistical analysis was performed using software SPSS, version 20.0. The quantitative data were expressed as mean value ± standard deviation (mean ± SD). Independent-sample t-test was used to evaluate the difference between control group and treatment group, matched t-test was used to evaluate the difference between before and after of treatment group, the receiver operating characteristic curve (TOC curve) was used to analyze sensitivity and specificity of diagnosis of (MV1-MV2)/ MV1, and Youden’s index was used to select optimal diagnostic value of cut-off. The level of statistical significance was set at P<0.05.

3. Results

3.1. Remisssive and relapse rate

Seventy patients with hyperthyroidism was treated with antithyroid drug, remisssive and relapse patients after drug withdrawal after 6 months were forty-four and twenty-six, respectively, and the relapse patients accounted for 37.1% of the total patients.

3.2. Peak systolic velocities

The peak systolic velocities of the patients at pretreatment and the end of therapy were (96.27±13.85) cm/s and (44.72±11.16) cm/s, respectively, there was significant difference between them (t=36.661, P<0.001). There was no significant difference between relapse patients and patients without relapse for peak systolic velocity of pretreatment (t=0.750, P=0.445). The peak systolic velocities of remissive and relapse patients at the end of therapy were (41.37±9.67) cm/s and (50.41±11.37) cm/s, respectively, there was significant difference between them (t=4.257, P<0.001), the peak systolic velocities of relapse patients and euthyroid subjects were (50.41±11.37) cm/s and (38.09±19.17), respectively, there was significant difference between them (t=4.485, P<0.001).

3.3. End-diastolic velocities

The end-diastolic velocities of the remissive and relapse patients at the end of therapy were (15.61±5.23) cm/s and (19.12±5.39) cm/s, respectively, there was significant difference between them (t=8.524, P=0.009). The peak systolic velocities of the relapse patients and euthyroid subjects at the end of therapy were (41.37±9.67) cm/s and (38.09±19.17), respectively, there was no significant difference between them (t=0.014, P=0.148).
3.4. Resistance index

The resistance index (RI) of the patients at pretreatment and the end of therapy were (0.64±0.06) and (0.62±0.06), respectively, there was significant difference between them (t=2.167, P=0.034). The RI of the remissive and relapse patients at the end of therapy were (0.62±0.05) and (0.61±0.06), respectively, there was no significant difference between them (t=0.295, P=0.602). The RI of pretreatment patients and euthyroid subjects were (0.64±0.06) & (0.60±0.05), respectively, there was no significant difference between them (t=2.569, P=0.012). The RI of the relapse patients and euthyroid subjects at the end of therapy were (0.61±0.06) and (0.60±0.05), there was no significant difference between them (t=-0.167, P=0.868).

3.5. MV1–MV2/MV1

The MV1-MV2/MV1 of the remissive and relapse patients were (0.57±0.07) and (0.47±0.09), respectively, there was significant difference between them (t=5.526, P<0.001).

3.6. ROC curve of peak systolic velocities of the superior thyroid arteries of relapse patients and euthyroid subjects

Area under ROC curve of peak systolic velocities of the superior thyroid arteries of relapse patients and euthyroid subjects was 0.773, the cutoff point was 40.3 cm/s, the Youden’s index was 1.496, and sensitivity and specificity were 84.6% and 65.0%, respectively.

3.7. ROC curve graph of MV1–MV2/MV1 of the superior thyroid arteries of remissive patients and relapse patients (Figure 3).

Area under ROC curve of MV1-MV2/MV1 of the superior thyroid arteries of remissive patients and relapse patients was 0.870, the cutoff point was 0.525, the Youden’s index was 1.556, and sensitivity and specificity was 86.4% and 69.2%, respectively.

3.8. Table 1 illustrates the peak systolic velocity of superior thyroid artery

End-diastolic velocity, resistance index, MV1-MV2/MV1 for pretreatment and the end of therapy hyperthyroidism patients, euthyroid subjects, remissive and relapse patients.

4. Discussion

The evaluation of therapeutic effect of antithyroid drug usually bases on follow-up findings of clinical symptoms and signs, laboratory tests of thyroid hormone (FT3, FT4) and thyrotropin stimulating hormone (TSH), etc. However, there is no ideal method for the prediction whether hyperthyroidism relapses after remission[1,2,4-7]. The relapse rate of antithyroid drug therapy for hyperthyroidism is relatively high, implying different conditions of hyperthyroidism, therapeutic course, patient age, inducing factors, etc[1,2]. There are different opinions about whether the intake of iodine relates to relapse of antithyroid drug therapy[14]. Struja et al[11] reported that the relapse rate after remission of antithyroid drug therapy is 48.7%, Wu-Xin et al[3] reported it is 42.5%, and the relapse rate of in this study is 37.1% (26/70). Shorter follow-up time (6 months) and different sample inclusion may be the reason that there was lower relapse rate after remission in this study.

The marked increasement of thyroid blood supply has been regarded as a characteristic of hyperthyroidism, and the elevated peak blood flow velocity of STA after effective drug therapy can return to the normal range. The thyroid gland is feeded by the superior thyroid artery and the inferior thyroid artery. The superior thyroid artery is the first branch of the external carotid artery and enters the thyroid upper pole. The inferior thyroid artery arises from the subclavian artery and eventually enters the thyroid lower pole. The superior thyroid arteries are easier to be detected during color Doppler flow imaging, so the superior thyroid artery was selected for evaluation in this study. The peak systolic velocity of superior thyroid artery in normal subjects has been reported inconsistently, ranging between (32.95±4.57) cm/s and (37±17) cm/s in majority of studies[12,13]. The peak systolic velocity of superior thyroid artery in this study is (38.09±9.17) cm/s.

In our study, there was no significant difference between remissive and relapse patients for the peak systolic velocities at pretreatment and remission at the end of therapy, there was significant difference between remissive and relapse patients for the peak systolic velocities at the end of therapy, and there was no significant difference between relapse patients and euthyroid subjects for the peak systolic velocities at the end of therapy. Which are similar to the results reported by Wu Xin et al[3], it indicates that changes of peak systolic velocity of superior thyroid artery can reflect the effect of antithyroid drug therapy in a certain extent, that the peak systolic velocity decreases to the normal range may be a reference indicator, which may associate with the prognosis and may be used as an indirect indicator for the assessment of antithyroid drug therapy, and it may provide useful information for the making of treatment regimen in follow-up. There was a significant difference between euthyroid subjects and relapse patients after treatment for the peak systolic velocities of STA in this study, suggesting that higher peak systolic velocities of STA at the end of antithyroid drug therapy may predict relapse after drug withdrawal. At the same time, there was significantly different between remission and later relapse patients of (MV1-MV2/MV1), suggesting that this may serve as a reference indicator for predicting relapse after antithyroid drug therapy. Both of these may predict the relapse of hyperthyroidism after drug treatment, but the sensitivity and specificity of the latter parameter are higher than the former (areas under the ROC curve are 0.870 and 0.773, respectively), indicating that the decrease rate of peak systolic flow velocity of STA after antithyroid drug therapy is more reliable to predict relapse.

Based on the results, it is not difficult to infer that if the laboratory tests and the peak systolic velocity of the superior thyroid artery after treatment return to normal, and the peak systolic velocity of the superior thyroid artery is lower than 40.3 cm/s or the decrease rate is lower than 0.525, then the probability to relapse after drug withdrawal is less, and vice versa. Therefore, the physician may predict the probability of relapse after drug withdrawal based on the decreased value of the peak systolic velocity of the superior thyroid artery and the decrease rate of the peak systolic velocity before and after treatment, to determine whether withdrawal or adjust the therapeutic regimen.

Compared with predicting relapse of antithyroid drug therapy, Technetium imaging[4], comprehensive evaluation based on multiple factors[5,8,9], thyroid stimulating antibody (TSAb) level assay[6], and thyroid stimulating antibody receptor chimera(Me4-TSAb) level assay[7], color Doppler ultrasound has advantages that it may determine the relative changes of the peak systolic velocity of the superior thyroid artery before and after treatment, better reproducibility, rational cost, free from radiation, and excellent compliance of patient.

Limitations of this study were that the sample size was small, the follow-up time was short (6 months) after withdrawal, not all types of hyperthyroidism were included, therefore, whether the conclusions are suitable for the prediction of relapses of all remissions of hyperthyroidism after antithyroid drug therapy needs to be further studied.
In conclusion, the relapse rate of hyperthyroidism increases when the peak systolic velocity of the superior thyroid artery is higher than 40.3 cm/s at the end of treatment or the decrease rate of peak systolic velocity (MV1-MV2/MV1) is lower than 0.525 at the end of treatment. Determination of the decrease rate of peak systolic velocity of superior thyroid artery before and after antithyroid drug therapy of hyperthyroidism may provide useful information for the prediction of hyperthyroidism relapse after remission.

<table>
<thead>
<tr>
<th>Pretreatment (n=70)</th>
<th>End of therapy (n=70)</th>
<th>Remission patients at the end of therapy (n=44)</th>
<th>Relapse patients at the end of therapy (n=26)</th>
<th>Health control (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak systolic velocity (MV) (cm/s)</td>
<td>96.27±13.85a</td>
<td>44.72±11.16a</td>
<td>41.37±9.677</td>
<td>50.41±11.370</td>
</tr>
<tr>
<td>End-diastolic velocity (EV) (cm/s)</td>
<td>35.16±8.697</td>
<td>19.12±5.390</td>
<td>15.61±5.23c</td>
<td>19.12±5.390</td>
</tr>
<tr>
<td>Resistance index (RI)</td>
<td>0.64±0.063</td>
<td>0.62±0.067</td>
<td>0.62±0.057</td>
<td>0.61±0.066</td>
</tr>
<tr>
<td>(MV1-MV2)/MV1</td>
<td>0.870</td>
<td>0.57±0.07f</td>
<td>0.57±0.07f</td>
<td>0.57±0.07f</td>
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References