Is it possible to diagnose Grave's disease with pulmonary hypertension on chest CT?

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Aims and objectives

Previous studies have suggested that loss of normal high attenuation in enlarged thyroid glands, thymic hyperplasia, and evidence of pulmonary hypertension on non-enhanced or enhanced CT, or echocardiography may occur in patients with Grave's disease.\textsuperscript{1-19} However, analysis of the diagnostic accuracy of each of the above CT findings has not been described in patients with Grave's disease with or without associated pulmonary hypertension. In general, the diagnosis of Grave's disease with pulmonary hypertension is based primarily on integrative analysis of clinical, laboratory, and echocardiographic findings. However, because a routine chest CT includes the thyroid glands, thymus, and heart, chest CT has the potential to diagnose Grave's disease with or without associated pulmonary hypertension in the absence of other information. Recently, we encountered several cases in which the diagnosis of Grave's disease with pulmonary hypertension was initially suggested based on chest CT findings, and ultimately confirmed by laboratory and echocardiographic findings.\textsuperscript{20} Thus, the purpose of this study was to evaluate the diagnostic accuracy of CT findings in patients with Grave's disease in the presence or absence of pulmonary hypertension in comparison with a control group.
Methods and materials

Study population

Fifteen consecutive patients with Grave's disease were retrospectively evaluated in this study. We analyzed clinical and radiological data of these patients at a university hospital between January 2006 and January 2016. We excluded two patients with Grave's disease who had underlying conditions that may lead to pulmonary hypertension [chronic obstructive pulmonary disease (n=1), pulmonary embolism (n=1)]. Thus, a total of 13 patients with Grave’s disease were included in the study. We divided the patients with Grave’s disease into two groups: group 1 (n=6), Grave’s disease with pulmonary hypertension and group 2 (n=7), Grave’s disease without pulmonary hypertension. As a control group, 17 age and sex matched patients with normal thyroid function tests (group 3) were enrolled during the same period. In all patients, thyroid function testing including autoantibody testing, chest CT, and echocardiography was performed within one month. Approval of the institutional review board was obtained and informed consent was waived for this study.

Laboratory and echocardiographic examination

A diagnosis of Grave’s disease was made if there was an increase in serum thyroid hormone [triiodothyronine (T3), normal range= 0.6-1.81 ng/ml; thyroxine (T4), normal range= 0.89-1.76 ng/ml] and thyroid stimulating hormone receptor antibody (TSH receptor antibody, normal range= 0-1.75 U/L), and decrease in TSH (normal range=0.35-5.5 ulU/mL). Pulmonary hypetension was defined as a systolic pulmonary artery pressure greater than 30 mmHg on transthoracic echocardiography. Systolic pulmonary artery pressure was measured in a resting state by the tricuspid regurgitation method using a modification of the Bernoulli’s equation on transthoracic echocardiography.¹⁸,¹⁹

CT technique
Non-enhanced and contrast enhanced chest CT were performed on 64-slice multidetector-row CT (MDCT) (Light-speed VCT, GE HealthCare, Milwaukee, WI, USA). Scanning parameters for chest CT were as follows: 120 kV, 200 mA, 0.625 mm collimation, 1.5 mm increment, 3 mm reconstruction. Sixty to 120 ml of intravenous Ioversol (Optiray 320 mg/ml, Tyco Healthcare, Montreal, Canada) was injected based on the patient’s body mass index. The scan range for chest CT was from the lower half of the neck to the adrenal glands.

**Image analysis**

Two radiologists (15-years of experience in cardiothoracic imaging and body imaging) who were blinded to clinical information independently analyzed the chest CT images. On an axial non-enhanced CT image, Hounsfield Unit (HU) values of the thyroid gland were measured in the left thyroid gland using as large as possible region of interest while avoiding calcification or low attenuation due to any thyroid nodule. We also measured the anterior-posterior diameter of both thyroid lobes on an axial contrast-enhanced CT image. Thyroid enlargement was defined as an anterior-posterior diameter of both thyroid lobes# 20 mm. For visual assessment of thyroid attenuation, on non-enhanced CT we divided thyroid attenuation into the three categories (Fig.1 and 2) and compared it with that of the adjacent neck muscle; 1. definite high attenuation of thyroid glands compared with adjacent neck muscle; 2. iso-attenuation of thyroid glands compared with adjacent neck muscle; 3. definite hypoattenuation of thyroid glands compared with adjacent neck muscle. We classified instances with inconspicuous attenuation difference between thyroid glands and adjacent neck muscle as grade 2. The thickness of thymus was measured as previously described. For visual assessment of the thymus, we divided thymic attenuation into four grades: 1. homogeneous soft tissue attenuation without fat; 2. inhomogeneous attenuation with soft tissue attenuation #70%; 3, inhomogeneous attenuation with soft tissue attenuation of 30%-70%; 4, homogeneous fat attenuation or inhomogeneous soft tissue attenuation<30%. For CT findings of the heart, the diameters of the both atria and ventricles, and main pulmonary artery were measured to evaluate for the presence of pulmonary hypertension on the axial enhanced CT image. The anterior-posterior diameter of the both atria and transverse diameter of both ventricles was measured at the level showing the largest dimension on an axial enhanced CT image. Specifically, the anterior-posterior diameter of the right atrium was measured from most posterior endocardial surface of the right atrium to the annulus of the tricuspid valve. The anterior-posterior diameter of the left atrium was measured from the most posterior endocardial surface to the most anterior endocardial
surface of the left atrium. The maximal diameter of the right and left ventricles was measured in the axial CT image showing tricuspid and mitral valve, respectively. The diameter of the right ventricle was measured from medial endocardial surface to the lateral endocardial surface perpendicular to the long axis at its basal portion, whereas the transverse diameter of the left ventricle was measured at its mid portion. If severe motion blurring obscured precise measurement of the right atrium or ventricle on CT, the measurement for this case was excluded. The transverse diameter of the main pulmonary artery was measured at the point of bifurcation of the main pulmonary artery into the right and left pulmonary artery on the appropriate axial enhanced CT image. For visual assessment of enlargement of the right atrium or ventricle, we classified their status in five grades: 1, definite enlargement of both right atrium and ventricle; 2, definite enlargement of one chamber and borderline enlargement of the other chamber (Fig.3); 3, borderline bilateral chamber enlargement; 4, borderline enlargement of one chamber and no enlargement of the other chamber; 5, no evidence of right chamber enlargement. After the full range of axial CT images was assessed, enlargement of the right atrium or ventricle was considered present if the subjective volume of the right atrium or ventricle was the same or larger compared with that of the contralateral side. A visual assessment of Grade 1-3 with respect to the right atrium and ventricle was deemed positive for the presence of pulmonary hypertension. Grades 4-5 were regarded as indicating absence of pulmonary hypertension. As an alternative way to determine the presence of pulmonary hypertension on CT, we used the diameter of main pulmonary artery #30 mm as a cutoff value. For analysis of the diameter as measured on CT, we used the mean value of the two radiologists. If there was disagreement on the visual assessment of the CT findings, a final decision was made by consensus reading.

Statistical analysis

Statistical analysis was performed using commercially available software (SPSS Inc., Chicago, IL, USA). All data were expressed as mean ± standard deviation for continuous variables and percentages or frequencies for categorical variables. Statistical analysis was performed using Fisher's exact or Chi-square test for categorical variables and Student's t-test for continuous variables, respectively. Kappa statistics were used for the evaluation of inter-observer variation of measurement of CT findings. A statistically significant difference was defined as p < 0.05.
**Fig. 1:** Grade 1 visual assessment of the thyroid glands on axial non-enhanced chest CT image-high attenuation of thyroid glands (arrowheads) compared with neck muscle (arrows) is noted at the level of thoracic inlet on an axial CT image.

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Fig. 2: Grade 2 visual assessment of the thyroid glands on axial non-enhanced chest CT image-isoattenuation of thyroid glands (arrowheads) compared with neck muscle (arrows) is noted at the level of thoracic inlet on an axial CT image.

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**Fig. 3:** 47-year-old man with typical CT findings of Grave's disease (iso-attenuation of diffusely enlarged thyroid glands compared with neck muscle) with pulmonary hypertension. Definite right atrial enlargement (RA) compared with the left atrium (LA) is noted at the level of the left atrium on axial CT image. Right pleural effusion is also noted. RV and LV indicate the right and left ventricle, respectively. Questionable right ventricular enlargement (RV) compared with the left ventricle (LV) is noted at the level of the LV on an axial CT image (not provided here).

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Results

There was a significant difference in the mean serum TSH receptor antibody levels between groups 1 and 2 (mean value, p=0.03). Otherwise, there was no significant difference in demographic characteristics or laboratory values between the three groups.

There was a significant difference in HUs of the thyroid glands on axial nonenhanced CT images between groups 1 and 3 (64.2 ± 9.5 vs 105.7± 14.4, p=0.00001) and groups 2 and 3 (68.7± 10.6 vs 105.7± 14.4, p=0.00001), but no difference between groups 1 and 2.

There was also a significant difference in the mean value of subjective thyroid attenuation between groups 1 and 3 (1.8 ± 0.4 vs 1.2 ± 0.4, p=0.02) and groups 2 and 3 (1.9 ± 0.4 vs 1.2 ± 0.4, p=0.01), but no difference between groups 1 and 2 (Table 2). Based on our use of iso-attenuation of diffusely enlarged thyroid glands compared with adjacent neck muscle on non-enhanced chest CT as a diagnostic indication of Grave’s disease, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 84.6%(11/13), 94.1%(16/17), 91.7%(11/12), and 88.9%(16/18), respectively.

For the thymic CT findings, there was no significant difference in the thickness of thymus among the three groups (group 1, 7.3 ± 8.0; group 2, 8.7 ± 6.1; group 3, 8.0 ± 6.5, p>0.05).

There was a significant difference in the mean value of the subjective classification of the thymus between groups 1 and 3 (2.2± 0.8 vs 3.7 ± 0.5, p=0.003) and 2 and 3 (2.6 ± 0.5 vs 3.7 ± 0.5, p=0.0006), but no difference between groups 1 and 2. Regarding CT findings of the cardiac chambers, we could not precisely measure the diameter of the right atrium in one patient in group 2 and two patients in the control group because there was significant motion artifact of the tricuspid valve on CT. Thus, cardiac measurements were excluded in these cases. There was no significant difference among the three groups in the mean diameter of the left atrium and ventricle. However, there was a significant difference in the mean diameter of the main pulmonary artery, the right ventricle, and the right atrium between groups 1 and 2 and groups 1 and 3, but not between group 2 and 3. For visual assessment of pulmonary hypertension based on enlargement of the right atrium or ventricle on CT, the sensitivity, specificity, PPV, and NPV of CT to predict pulmonary artery hypertension in comparison to echocardiography was 100%(6/6), 87.5%(21/24), 66.7%(6/9), and 100%(21/21), respectively. Using a transverse diameter of main pulmonary artery ≥30 mm as a cutoff value for the presence of pulmonary hypertension on enhanced axial chest CT, the sensitivity, specificity, PPV, and NPV to predict pulmonary hypertension on echocardiography were 100%(6/6), 75%(18/24), 50%(6/12), 100%(18/18), respectively. Kappa values of the diameter measurements of the CT findings ranged from moderate to good (0.4-0.8). The Kappa value of the visual assessment of the thyroid glands and heart was higher than that of visual assessment of the thymus and the diameter measurement of the thyroid glands, thymus, and heart.
Conclusion

In conclusion, iso-attenuation of diffusely enlarged thyroid glands on nonenhanced CT is a good indicator for the presence of Grave's disease, whereas thymic hyperplasia is minimal in most patients with Grave's disease. Because there is a significant difference in the diameter of the right atrium and ventricle between the patients with Grave's disease with pulmonary hypertension and those without, chest CT has the potential to diagnose Grave's disease as a cause of pulmonary hypertension prior to any other testing.
References

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