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Potential risk factor of Graves' orbitopathy among Chinese patients: A clinical investigation.

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Abstract

Objective: To identify predictive factors that can be used in screening the healthy subjects who are at high risk of developing Graves' orbitopathy

Materials and methods: We have reviewed the medical records of healthy Chinese subjects with Graves' disease visited at Department of Ophthalmology, Wuxi Second People's Hospital, Jiangsu, China between March 2005 to March 2015. We used computerized database of Wuxi Second People's Hospital to collect medical records of Chinese subjects with and without Graves' orbitopathy to identify the potential risk factor of Graves' orbitopathy, and data were analyzed by univariate analysis.

Result: Medical records of 2,500 patients with Graves' disease who had visited during March-2005 to March 2015. Of 2,500 patients, 1500 (60%) patients had Graves' orbitopathy, and 1,000 (40%) patients had no Graves' orbitopathy. Incidence of Graves' orbitopathy was significantly higher in patients who were smoker than non-smoker. We also observed that the stress was significantly higher in patients with Graves' orbitopathy than the patients without Graves' orbitopathy. Family history of thyroid disease was significantly higher in patients of Graves' orbitopathy group when compared to patients without Graves' orbitopathy. The level of thyroxin (free form), triiodothyronine (free form), thyroid stimulating hormones receptor antibodies, and antiperoxidase antibodies were significantly higher among patients of Graves' orbitopathy when compared to the patients with Graves' diseases without orbitopathy.

Conclusion: We suggest alternation thyroid hormones (thyroxin (free form) and triiodothyronine (free form) and thyroid antibodies (thyroid stimulating hormones receptor antibodies and antiperoxidase antibodies) are important predictors of Graves' orbitopathy among Chinese subjects.

Keywords: Thyroid stimulating hormones, Graves' disease, Graves' orbitopathy.

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Introduction

Graves' disease (GD) is a polygenic multifactorial autoimmune disease, occurs in approximately 3-11 per 1000 people in Chinese populations [1]. GD is characterized by thyroid hyperplasia and excessive thyroid hormone release, involving production of autoantibodies against thyroid-stimulating hormone receptor (TSHR) and hyperthyroidism fallowing lymphocytic infilteration of the thyroid. Graves' disease is caused by interaction between genetic factors and/or environmental factors viz. smoking, anxiety, bacterial and viral infections [2-4] leads to activation of the innate immunity. Graves' ophthalmopathy is an extrathyroidal disorder found in 25-50% of individuals suffering from GD [5]. General clinical sign includes periorbital oedema, sight-threatening corneal ulceration and even blindness [6,7].

Graves' orbitopathy significantly affect quality of life due to unavailability of effective treatment modalities. Currently, limited treatment options of graves' orbitopathy are available with variable efficiency profile of available treatment options. Several lines of clinical evidences showed that Graves' ophthalmopathy has negative impact on quality of life and causes behavior syndromes and emotional stress because of scarring eye signs [8-10]. A study has shown that the individuals with graves' orbitopathy have higher risk of disability related to work and joblessness [11].

Since etiology of Graves' orbitopathy is remain unclear in spite of several efforts to find the potential reasons, thus there was no established and effective methods to prevent the Graves' orbitopathy. Therefore, identification of potential risk factor in development of PE helps to prevent incidence of Graves' orbitopathy. The risk factor of Graves' orbitopathy in healthy Chinese subject was not evaluated earlier. Therefore, we designed this study to assess risk factor of Graves' orbitopathy among healthy Chinese subjects women. We also evaluated the relationship between Graves' orbitopathy and family history of thyroid disease. The objective of present study was to identify predictive factors that can be used in screening the healthy subjects who are at high risk of developing Graves' orbitopathy, this may help in reducing the incidence of Graves' orbitopathy related morbidity and mortality in pregnant women.

Materials and Methods

We reviewed the medical records of healthy Chinese subjects with Graves' disease and visited at Department of Ophthalmology, Wuxi Second People's Hospital, Jiangsu, China from March 2005 to March 2015 for treatment. We used computerized database of Wuxi Second People's Hospital to collect medical records of Chinese subjects with and without Graves' orbitopathy to identify the potential risk factor of Graves' orbitopathy. We have excluded the medical records of subjects who had diabetes, history of chronic hypertension or any other systemic disease excepting Graves' disease with or without Graves' orbitopathy. Institutional ethics committee approval was obtained from Wuxi Second People's Hospital. Since, this was a retrospective, observational chart review study, and none of patients whose medical records reviewed were contacted, the requirement for obtaining formal informed consent was waived by ethics committee.

As per the protocol of our hospital, all the patients who visited for consultation of Graves' disease were underwent laboratory and physical examination. The subject who had increased concentration of free thyroxin, free triiodothyronine, and thyroid - stimulating hormone (TSH) receptor antibodies with ultrasound evidence of goiter were diagnosed as Graves' disease by endocrinologist. We have also noted the following key determinant of development of Graves' disease and its associated diseases from medical record of each patient: Age at the time of development of Graves' disease; gender; plasma level of free triiodothyronine; free thyroxin; antibodies of TSH receptor, antiperoxidase and thyroglobulin; size of goiter; previous treatment and ocular findings after development of Graves' disease. Size of thyroid was graded according to WHO criteria for all patients who visited our hospital. All the patients who visited our hospital for treatment of Graves' disease were directed to complete questionnaires for Ophthalmological assessment as per the requirement of European Group on Graves' Orbitopathy. Medical records of each patient with and without Graves' orbitopathy. As a routine procedure of our hospital, blood sample was collected from each patient for hormonal assay and measured by different immunoassay. All the laboratory measurement for detection of antibodies was performed according to manufacturer's instruction.

Data from each patient was coded and analyzed using Graph Pad Prism statistical analysis software (version 6.0). Quantitative variable was presented as mean ± standard deviation, and data were compared using parametric/non-parametric statistical test based number of comparison group and distribution of data, using 2 sided statistical tests. Normality test (Kolmogorov-Smirnov test or Shapiro-Wilks test) will be used to check the distribution of data of quantitative data. Categorical variables was presented as absolute number and/or percentage of subjects in each category, and were compared using Chi-square or fisher exact test based on size of data, using 2 sided statistical tests.

Result

We have reviewed medical records of 2,500 patients with Graves' disease who had visited during March-2005 to March 2015 in our hospital. Of 2,500 patients, 1500 (60%) patients had Graves' orbitopathy, whereas 40% (1000/2500) of subjects had no Graves' orbitopathy. The average age at the onset of Graves' disease was higher in patients with Graves' orbitopathy than patients without Graves' orbitopathy. On comparing BMI, significantly higher proportions of overweight patients (25-29 kg/m^2) were in Graves' orbitopathy group as compared to patients without Graves' orbitopathy. This indicates that the majority of patients with Graves' orbitopathy were overweight (Table 1). Gender distribution among both the subgroups was also found similar, with the higher proportion of male patients in Graves' orbitopathy group as compared to patients without Graves' orbitopathy. There was no statistical significant difference in terms of number of year of education was observed among both the groups ($p>0.05$). Demography and baseline characteristic of patients Graves' disease are presented in Table 1.

Table 1. *Demography and clinical characteristic of patients Graves' disease.*

Variables	Individuals with Graves' disease N=2,500	
	Graves' orbitopathy (N=1500)	Without Graves' orbitopathy (N=1,000)
Age categories		
18 or less	15%	5%
Between 19-34	65 %	90%
More than 35	20%	5%
Age (year), Mean (SD)	29 (5.2)	28(4.3)
Weight (kg) Mean (SD)	83 (3.7)	71(3.6)
BMI categories		
Overweight (25-29 kg/m^2)	45%	5%
Non-overweight (20-24 kg/m^2)	55%	95%
Smoking status		
Smoker	38%	12%
Non-Smoker	62%	88%
Gender		
Female	30%	30%
Male	70%	70%

Values are expressed as % of subjects in each category except age and weight. N=Total number of subject in each group.

Incidence of Graves' orbitopathy was significantly higher in patients who were smoker than non-smoker. We also observed that the stress was significantly higher in patients with Graves' orbitopathy than the patients without Graves' orbitopathy. Family history of thyroid disease was significantly higher in

patients of Graves' orbitopathy group when compared to patients without Graves' orbitopathy. Higher risk of Graves' orbitopathy was found in patients with family history of thyroid disease as compared to patients with no family history of thyroid disease. Family history of thyroid disease was significantly higher in patients of Graves' orbitopathy group when compared to patients without Graves' orbitopathy. This indicates that the higher risk of Graves' orbitopathy was found in patients with family history of thyroid disease as compared to patients with no family history of thyroid disease. Incidences of drug-induced hypothyroidism were significantly higher in Graves' orbitopathy group than patients without Graves' orbitopathy. High proportions of patients in Graves' orbitopathy group were smokers when compared to group with no Graves' orbitopathy. Similar trend was observed for stress parameters, the stress was significantly higher in patients with Graves' orbitopathy when compared to patients of Graves' diseases without orbitopathy. There was no effect of work atmosphere on development of orbitopathy among patients with Graves' diseases (Table 2).

Table 2. *Environmental risk factor of graves' orbitopathy among patients with Graves' diseases.*

Environmental risk factor	Graves' orbitopathy (N=1500)	Without Graves' orbitopathy (N=1000)	P value
Family history of thyroid disease			
Present	45%	5%	<0.0001
Absent	55%	95%	
Weight Loss			
Present	40%	8%	<0.0001
Absent	60%	92%	
Drug-induced hypothyroidism			
Present	35%	9%	<0.0001
Absent	65%	91%	
Smoking			
Present	38%	12%	<0.0001
Absent	62%	88%	
Stress at home			
Present	31%	11%	<0.0001
Absent	69%	89%	
Stress full work environment			
Present	32%	4%	<0.0001
Absent	68%	96%	

Values are expressed as % of subjects in each category. N=Total number of subject in each group. P value calculated by chi-square test using multivariate analysis.

The size of thyroid gland during palpitation was significantly bigger in patients with orbitopathy when compared in patients without orbitopathy. The level of thyroxin (free form), triiodothyronine (free form), thyroid stimulating hormones receptor antibodies, and antiperoxidase antibodies were significantly higher among patients of Graves' orbitopathy when compared to the patients with Graves' diseases without orbitopathy (Table 3). We found that the risk of orbitopathy was double in patients who had family history of Graves' orbitopathy and among chronic smoker than patients with no family history of Graves' orbitopathy, and non-smoker. Our study results shown that the following potential factors are involved in etiology of Graves' orbitopathy: Age, Gender, family history of Graves' diseases with orbitopathy; previous exposure of drug lead to thyroid dysfunction; smoking; obesity; thyroid gland size during palpitation; stress; hormones level (thyroxin and triiodothyronine); antibodies against thyroid stimulating hormones receptor, and antiperoxidase antibodies.

Table 3. *Thyroid hormone and antibodies related of abnormality in causing graves' orbitopathy among patients with Graves' diseases.*

Variable	Graves' orbitopathy (N=1500)	Without Graves' orbitopathy (N=1,000)	Odd ratio 95% CI P value
Free thyroxin (in pmol/L)			
Abnormal	45%	5%	15.54 5.82-41.49 <.0001
Normal	55%	95%	
Free triiodothyronine (in pmol/L)			
Abnormal	35%	9%	5.44 2.44-12.10 <.0001
Normal	65%	91%	
Thyrotropin (in mU/L)			
Abnormal	38%	12%	4.49 2.17-9.28 <.0001
Normal	62%	88%	
Antiperoxidase antibodies (in kU/L)			
Abnormal	40%	8%	7.66 3.35-17.50 <.0001
Normal	60%	92%	
TSH receptor antibodies (in U/L)			
Abnormal	45%	5%	15.54 5.82-41.49 <.0001
Normal	55%	95%	
Antibodies against thyroglobulin (in kU/L)			
Abnormal	40%	8%	7.66 3.35-17.50 <.0001
Normal	60%	92%	

Values are expressed as % of subjects in each category. P value calculated by chi-square test using multivariate analysis. N=Total number of subject in each group.

Discussion

This was the first largest retrospective case control study to determine the potential risk of Graves' orbitopathy among healthy Chinese subjects. Since etiology of Graves' orbitopathy is remain unclear in spite of several efforts to find the potential reasons, thus there was no established and effective methods to prevent the Graves' orbitopathy. Therefore, identification of potential risk factor in development of PE helps to prevent incidence of Graves' orbitopathy. The risk factor of Graves' orbitopathy in Chinese subject was not evaluated earlier. Therefore, we designed this study to assess risk factor of Graves' orbitopathy among healthy Chinese subjects women. We also evaluated the relationship between Graves' orbitopathy and family history of thyroid disease. The objective of present study was to identify predictive factors that can be used in screening the healthy subjects who are at high risk of developing Graves' orbitopathy, this may help in reducing the incidence of Graves' orbitopathy related morbidity and mortality in pregnant women.

Our finding showed that patients with family history of graves' orbitopathy were at higher risk of developing orbitopathy. Our study showed positive relationship between smoking and graves' orbitopathy, and our finding was consistent with previous findings [12]. Our study suggested the risk of developing Graves' orbitopathy was significantly higher in patients with high plasma concentration of TSH receptor antibodies and free thyroxin, this indicates the role of TSH and thyroxin in development of Graves' orbitopathy. TSH receptor is known autoantigen in development of graves' diseases, and also involved in graves' orbitopathy [13]. Overexpression of TSH receptor was reported in patients of Graves' orbitopathy who had high orbital fat as compared to non-obese patients [13]. The level of thyroxin (free form), triiodothyronine (free form), thyroid stimulating hormones receptor antibodies, and antiperoxidase antibodies were significantly higher among patients of Graves' orbitopathy when compared to the patients with Graves' diseases without orbitopathy.

In the past decades, many laboratory tests has been advised to discover the potential risk of developing Graves' orbitopathy, however, such as lab investigations have inadequate sensitivity and costly which was difficult to afford. Thyroid antibodies (thyroid stimulating hormones receptor antibodies and antiperoxidase antibodies), mental stress, smoking, obesity are amendable and avoidable risk factor of Graves' orbitopathy, whereas family history of graves' disease with orbitopathy even could not be modifiable, nonetheless very useful to identify the patients who are at higher risk of Graves' orbitopathy and need more attention. This help in reducing the incidence of Graves' orbitopathy related morbidity and mortality in patients with Graves' disease. We encourage increasing awareness of risk factor of Graves' orbitopathy, which could lead to decrease prevalence of Graves' orbitopathy among healthy subjects.

Conclusion

We suggest alternation thyroid hormones (thyroxin (free form) and triiodothyronine (free form) and thyroid antibodies (thyroid stimulating hormones receptor antibodies and antiperoxidase antibodies) are important predictors of Graves' orbitopathy among Chinese subjects. Other factors include mental stress; smoking, obesity and family history of graves' diseases are considered as key predictors of Graves' orbitopathy among Chinese subjects. These prognostic factors can be used in screening the patients with Graves' diseases women who were at high risk of developing Graves' orbitopathy. This finding helps in reducing the incidence of Graves' orbitopathy related morbidity and mortality in patients with Graves' diseases. We encourage increasing awareness of risk factor of Graves' orbitopathy, which could lead to decrease incidences of Graves' orbitopathy among patients with Graves' diseases.

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