

Occupational Stress and its Relation to Grave's Disease

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Abstract

Background: Graves' disease is an autoimmune thyroid gland disease that causes increased activity of the thyroid hormones. But, the mechanism by which the autoantibodies are generated is still unclear. Some theory suggests that daily life stress may be a risk factor that triggers Graves' disease. The aim of this report is to enrol a systematically searching in order to get an answer about the risk factor of the Grave's disease and the prevention measure.

Methods: In this case report, a 47-year-old career woman with prominent occupational stress was diagnosed with Graves' disease. Literature searching was done on database such as Pubmed, Cochrane Library, and Science Direct with occupational stress, stressful life event, and Graves' disease as the keywords. One article was selected and critically appraised.

Results: One case-control study showed that patients with Graves' disease had odds ratio (OR) of having stressful life events as big as 8.59; 95%CI = 2.35-20.80, and the number needed to harm (NNH) is 2.35.

Conclusion: Occupational stress is a prominent risk factor for developing Graves' disease. However, this is based on one article

Key words: Graves' disease, occupational stress

Abstrak

Latar Belakang: Penyakit Graves merupakan penyakit autoimun pada kelenjar tiroid yang menyebabkan peningkatan aktivitas hormon tiroid. Namun, mekanisme mengenai bagaimana autoantibodi tersebut terbentuk belumlah jelas. Beberapa teori menyatakan bahwa stress pada kehidupan sehari-hari dapat menjadi faktor risiko yang mencetuskan terjadinya penyakit Graves.

Metode: Pada laporan kasus ini, seorang wanita pekerja berusia 47 tahun dengan stress okupasi yang prominen didiagnosis dengan penyakit Graves. Pencarian literatur dilakukan pada database Pubmed, Cochrane, dan Science Direct dengan menggunakan kata kunci occupational stress, stressful life event, dan Graves' disease. Pencarian menghasilkan satu artikel terpilih yang kemudian ditelaah kritis.

Hasil: Satu studi kasus-kontrol menunjukkan bahwa pasien dengan penyakit Graves mempunyai odds ratio (OR) untuk mengalami kejadian stress dalam kehidupan sebesar 8.59, sedangkan number needed to harm (NNH) yang diperoleh sebesar 2,35.

Kesimpulan: Stress okupasional merupakan faktor risiko yang penting dalam menyebabkan penyakit Graves.

Kata kunci: penyakit Grave's, stress okupasi

Introduction

Hyperthyroidism refers to increasing activity of the thyroid gland, which then causes increase in thyroid hormone circulating in the blood. Hyperthyroidism can be categorized as primary and secondary. Primary hyperthyroidism is caused by problems arising in the thyroid gland itself, mainly Graves' disease, toxic multinodular goiter, or follicular adenoma¹. Graves' disease is the most common cause of hyperthyroidism, with an annual incidence of 20 to 50 cases per 100,000 persons. The incidence peaks between 30 and 50 years of age, but people of any age can be affected. Women are more susceptible to Graves' disease, with 3% lifetime risk compared to 0,5% for men.²

Graves' disease was first reported in the 19th century. At that time, a woman came complaining that she felt extremely frightened without any real injury. Physical examination only revealed palpitation, swelling of the thyroid gland, and the patient felt anxious.^{2,3} Discovery of thyroid stimulating hormone (TSH), thyroid hormone, and autoimmune disease in later years then explained the pathophysiology of Graves' disease. In the most current theory, autoantibodies directed against thyrotropin receptors are produced in Graves' disease. These antibodies mimic the action of thyrotropin (TSH) at its receptor, which then stimulate thyroid hormone production that is uncontrolled by the hypothalamic-pituitary axis. Increasing level of thyroid hormone causes increase in the body's rate of metabolism and produces manifestations such as weight loss, palpitations, tremor, increased sweating, hair loss, anxiety, insomnia, proptosis, etc.^{1,3,4}

However, until today, the exact mechanism in which the autoantibodies are generated is still unclear. Many scientists believe that stress is the trigger to this disease, and it also plays a role in the effectiveness of the treatment⁵. Several pathogenesis mechanisms have been proposed, which may involve glucocorticoids and catecholamines (also known as stress hormones).^{2,5} Therefore, in this evidence-based case report, the author would like to find out whether there is association between occupational stress and hyperthyroidism.

Case Description

A woman, 47 years old, came to an occupational health clinic with chief complaint of abrupt weight loss.

She noticed that her weight had gone down by more than 5 kilograms in the last 2 months. The woman also complained about tremor in both of her hands, sweating even though the air temperature is cool, and she also often felt her heart pounding and felt agitated. These symptoms first occurred 6 months ago, and the patient never received any treatment before. These kinds of symptoms were never experienced by the patient before. No significant data was obtained in the family history and past medical history. There was no record of malignancy or other metabolic diseases in the patient. One year prior to the case, the patient was diagnosed with pelvic inflammatory disease and was properly treated. The patient never engaged in alcoholism or smoking.

Physical examination of the patient revealed slight tachycardia (110 beats per minute), normal blood pressure, body temperature, and respiratory rate. Slight tremor was found in both upper extremities. Slightly diffuse goiter was found and examination with the stethoscope revealed no bruit. Proptosis was not found in the patient. Other physical examinations revealed results within normal range. Blood laboratory examination was then conducted on the patient. Low level of thyroid-stimulating hormone was found (less than 0.0025 mIU/l), with high level of free T₄ and T₃ (8.61 ng/dl and 2.39 pg/dl respectively). The patient also has low level of plasma vitamin D (28 ng/ml). The patient was then diagnosed with diffuse toxic goiter (Graves' disease) and started consuming methimazole 10 mg once a day.

Apart from her medical history, the patient is an accountant, currently being the Head of Accounting Division of an oil and gas industry. She mostly spent her working hours in the office sitting and doing office work, auditing, and doing several meetings internally and also with external parties. The patient was known as a high-achiever and well-performed worker in the industry. She would not leave the office until her target was achieved causing her to come home late. There was no other significant stress in the patient's history, the patient had a happy family and she has no financial issues. The patient then wondered and asked the doctor, whether the occupational stress she received might be the cause of her disease. Based on the case illustration, a clinical question is developed: In adults with productive age, is there an association between occupational stress and Graves' disease?

Evidence

Literature searching was done using several online databases, which are Pubmed®, Cochrane Library®, and Science Direct. The literature searching was done using “Graves’ disease” and “occupational stress” as the main keywords. The searching strategy flow chart can be seen on Figure 1, while searching keywords used on each database can be seen on Table 1.

In the first stage, articles were found from three different databases, using “occupational stress” and “Graves’ disease” as the main keywords. Several synonyms for the term “occupational stress” were also used, such as “job stress” or “stress at work”. The searching strategy resulted 44 articles from Pubmed,

1 article from Cochrane, and 3 articles from Science Direct. From those search results, the articles were filtered based on inclusion criteria that has been decided: the article is in English, full text is accessible, and the study is cohort study, case-control study, or systematic review and meta-analysis study. Afterwards, filtering double was done, and the author excluded studies which were not relevant or not done on adults on productive age. From that process, 1 article remained, then its abstract and full text were read. This article was then selected for critical appraisal. The article was then critically appraised using Oxford Centre for Evidence Medicine criteria for etiological studies. The critical appraisal was done from validity, importance, and applicability aspect.

Table 1. Searching Keywords Used on Several Databases

Database	Searching Strategy	Result
Pubmed	((graves disease) OR (hyperthyroidism)) AND (((occupational stress) OR (job stress)) OR (stress at work))	44
Cochrane	occupational stress in All Text AND “Graves’ disease” in All Text	1
Science Direct	occupational stress AND graves’ disease	3

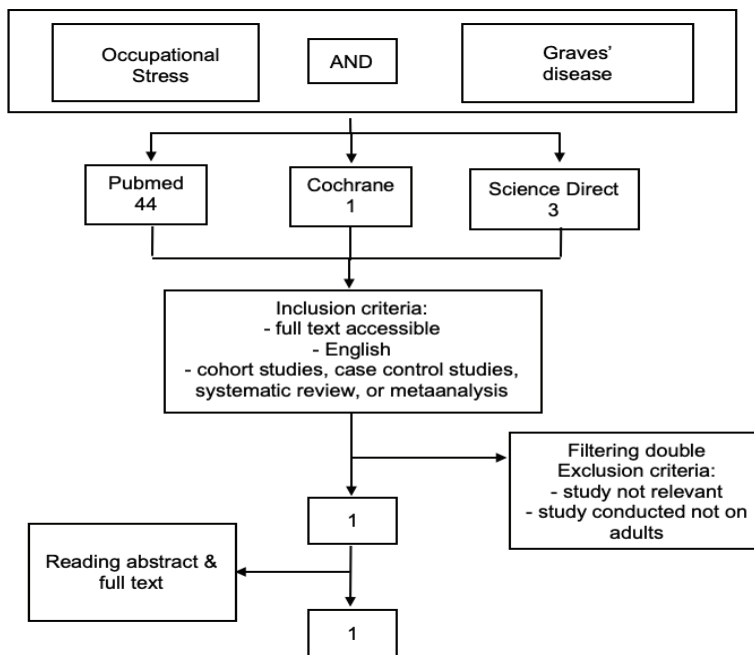


Figure 1. Literature searching flow chart

Result

Based on the searching strategy and article selection conducted by the authors, only one study was chosen and critically appraised. It is a study conducted by Radosavljevic et al⁶. The result of the critical appraisal can be seen in Table 2.

The chosen article was written by Radosavljevic, 1996. It was a case control study with the sample amount of 200. This study has strength by having the big number of samples and also differentiates occupational stress from other stressful like events. However, the weakness of this study that the population was from Yugoslavia. During the time of the study, it was mentioned that the impact of war is neighbouring countries and economic deterioration may influence the study result.

The study conducted Radosavljevic et al. is a case-control study that recruited Graves' disease patients, and then compared it with control subjects that were matched according to several criteria such as age, sex, etc. Both

the patients and controls were then assessed whether they have occupational stress in their life 12 months prior to being diagnosed with Graves' disease. Study Radosavljevic et al. used Paykel's Interview for Recent Life Events. The study asked about occupational stress that were experienced by the subjects during the last 12 months prior to being diagnosed with Graves' disease.

The result from Radosavljevic et al. study shows a quite high OR (OR 8.59; 95%CI = 2.35-20.80), which means that stressful life events, mainly occupational stress in this study, is a much greater risk for causing Graves' disease. In the discussion section of the Radosavljevic et al. article, the author mentioned that the more impactful result from the study could be caused by the fact that the country (Yugoslavia) at that time was greatly affected by war of the neighbouring countries and also the country was undergoing economic deterioration, therefore might cause the OR to be higher. Based on the odds ratio in this study, it is estimated that people with Graves' disease will be 8,59 times more likely to have experienced occupational stress.

Table 2. Critical Appraisal Using Oxford Centre for Evidence Medicine Criteria

Validity	Radosavljevic, 1996
Were there clearly defined groups of patients, similar in all important ways other than exposure to the treatment or other cause?	Yes, the group was clearly defined and the control group subjects were also matched with the patients with Graves' disease for age (up to 2 years difference), sex, and type of residence.
Were treatment exposures and clinical outcomes measured the same ways in both groups (e.g., was either objective or blinded to exposure)?	All subjects from both groups undergone the same examination in the same medical centre and the same laboratory. But it was not mentioned whether the interview was done by the same interviewer or not. The instrument used for this research was Paykel's Interview for Recent Life Events.
Was the follow-up of study patients complete and long enough?	The follow-up was long enough, since the questionnaire asked about any stressful life events 12 months prior to the diagnosis of Graves' disease.
Is it clear that the exposure preceded the onset of the outcome?	Yes, the questionnaire clearly stated that the life events reported in the questionnaire were events happening up to 12 months preceding the diagnosis. People with prior history of Graves' disease were already excluded in the beginning of the sample selection.
Is there a dose-response gradient?	This study did not analyse about dose-response gradient.
Is there positive evidence from a dechallenge-rechallenge study?	It is not possible to be done in this case.

Is the association consistent from study to study? It is unknown, as there was only one study found.

Does the association make biological sense? Yes. Theoretically, psychological stress may increase the level of stress hormones in human body (catecholamines and glucocorticoids). Current hypothesis states that stress hormones may induce the formation of autoantibodies responsible for Graves' disease.

Exposure and outcome table

Exposure	Outcome	
	+	-
+	21	3
-	79	97

Odds ratio (OR) 8.59; 95% CI = 2.35-20.80

Exposure event rate (EER), Control event rate (CER), Absolute risk increase (ARI) and Number needed to harm (NNH) This is a case-control study, so EER cannot be calculated

Can the study results be extrapolated to your patient? Yes

What are your patient's risk of the adverse outcome? Based on the odds ratio in this study, it is estimated that people with Graves' disease will be 8.59 times more likely to have experienced stressful life events in the occupation sector, 12 months prior to being diagnosed with Graves' disease.

Discussion

Based on one case control study by Radosavljevic et al., we can see that people with Graves' disease are more likely to have experienced occupational stress about 12 months before the person was diagnosed with Graves' disease; with the odds ratio being pretty high (OR 8.59). This study shows that there may be causal relationship between occupational stress and the occurrence of Graves' disease. As the theory suggests, people with stressful life events will experience higher psychological stress. Naturally, psychological stress will trigger hormone imbalance in human body, which causes the secretion of hormone level to increase, namely catecholamines and glucocorticoids. The exact mechanism by which these stress hormones cause Graves' disease is still unknown, but current hypothesis states that increased level of stress hormones may induce the formation of autoantibodies which are responsible for causing Graves' disease.⁷⁻⁹

Research conducted by Sonino et al. in 1993 and Kung et al. in 1995 show that people with Graves'

disease have higher risk of having experienced stressful life events prior to being diagnosed with the disease.^{10,11} Although general stress is quite well-known to be the risk factor for Graves' disease, little research was conducted to classify what kind of stress is responsible for developing Graves' disease in a patient. As it was shown in this literature searching, only one study specifically analysed the relationship between occupational stress and Graves' disease. The small number of evidence may be a weakness in this report, but the population in Radosavljevic study is highly similar with the conditions found in our patient. The patient is a career woman with prominent occupational stress and was diagnosed with Graves' disease.

This clearly shows that the patient had obvious occupational stress. There was no other stress found in this patient, she had a happy family and no financial problem. No other significant medical history related to thyroid disease was found in this patient, so the most possible trigger for this patient to acquire Graves' disease is stressful life event, mainly from the occupational stress. And then, based on the literature searching and

critical appraisal, it was also revealed that occupational stress is a significant risk factor for developing Graves' disease. Therefore, this patient should receive proper treatment for her disease and receive anti-thyroid drugs. The patient should also be reminded that too much occupational stress can contribute to her disease and she should manage this occupational stress that she had.

Conclusion

Study on the relationship between occupational stress and Grave's disease is very limited; only one case-control study showed that people with Graves' disease had increased risk for occupational stress. Although based on the study we may concluded that occupational stress is a significant risk factor for a patient to develop Graves' disease, further research is still needed to confirm the relationship between occupational stress and Graves' disease.

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