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Main Article

Reinke's oedema, hormones and hormone replacement therapy

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Abstract

Objective: To study the implications of hormone replacement therapy (HRT) treatment in the pathogenesis of Reinke's oedema (via a possible pseudo-hypothyroidism effect), and also to study why the disease affects a predominantly post-menopausal female population.

Design: Prospective case series study.

Setting: Two teaching hospitals and two district general hospitals in Scotland, UK.

Subjects: Thirty-three patients diagnosed with Reinke's oedema who presented in the out-patient department before or after treatment.

Results: Thyroid function tests were normal in all but two cases. Only three patients were receiving HRT treatment.

Conclusions: The study produced no evidence to support a relationship between HRT treatment and the pathogenesis of Reinke's oedema; this supports previous studies which concluded that thyroid function was not related to the development of Reinke's oedema. Some new ideas regarding hormonal factors in Reinke's oedema are discussed.

Key words: Larynx; Oedema; Hormone Replacement Therapy, Post-Menopausal; Thyroid Function Tests

Introduction

Reinke's oedema is a relatively rare disorder. In a representative series of benign pathology excised from the vocal folds, Reinke's oedema comprised 6 per cent of the pathologic specimens removed.[1] It affects mainly middle-aged women who smoke, and understanding of the pathogenesis is limited despite extensive research.

Reinke's oedema is an accumulation of fluid in the superior aspect of the superficial layer of the lamina propria (SLLP) along the entire length of the membranous fold. It remains localized because of dense anterior and posterior fibrous tissue connections and poor lymphatic supply. It is almost always bilateral but may be asymmetrical.

It is well documented that smoking is a significant factor in the pathogenesis of Reinke's oedema, but an explanation as to why the disease occurs predominantly in post-menopausal women remains elusive.

A search of the literature revealed controversial evidence on the role of thyroxine and a paucity of information on the effect of hormone replacement therapy (HRT) on the pathogenesis and progress of the disease.

Because of its hepatic first pass effect, oral oestrogen therapy raises the levels of circulating thyroxine-binding globulin, thereby increasing the bound fraction and decreasing the free (bioactive) fraction of circulating thyroxine.[2] It is therefore possible that HRT may be creating a pseudo-hypothyroidism effect which may contribute to the pathogenesis of Reinke's oedema.

The purpose of this study was to try to clarify further the effect of hormones in the pathogenesis of Reinke's oedema, to attempt to identify the role of HRT (if any) and to explore new theories as to why this disease is confined mainly to post-menopausal women.

The present, prospective study was of 33 patients presenting to ENT departments within the Lothian, Fife and Tayside regions of Scotland, diagnosed with Reinke's oedema, between April 2004 and January 2005.

Materials and methods

Patients visiting an out-patient department before or after a cordotomy operation were identified and

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completed a brief verbal questionnaire in the form of an interview. The questions covered epidemiological data, smoking habits, whether the patient was post-menopausal or not, whether they had had a hysterectomy or not, and whether they were receiving HRT treatment.

Thyroid function tests were performed on all subjects.

There were no age limits and the only exclusion criterion was male gender.

Results

The four hospitals which provided patients for this study served a population of approximately 1 000 000 people.

During the period of the study, 33 patients were operated upon or seen in out-patients and supplied the clinical material for this study. All 33 patients were of Caucasian origin. Three men were diagnosed with the condition during the period of the study but were excluded.

The average age of the patients was 57 years (range, 41 to 79 years). The definition of hypothyroidism was an increased thyroid-stimulating hormone (TSH) concentration and a decreased free thyroxine (T4) concentration, compared with a normal range for TSH of 0.5–3.9 mU/l and for T4 of 10–19 pmol/l. Small variations existed between different laboratories.

All 33 patients were smokers.

Thirty of the 33 (91 per cent) patients were post-menopausal. Only three had undergone a hysterectomy.

Three patients (nine per cent) were receiving HRT treatment (Figure 1).

Only two patients (six per cent) demonstrated slightly abnormal thyroid function tests; both had a slightly low TSH concentration, and one was known to be suffering from Hashimoto disease. In both cases, the T4 concentration was normal.

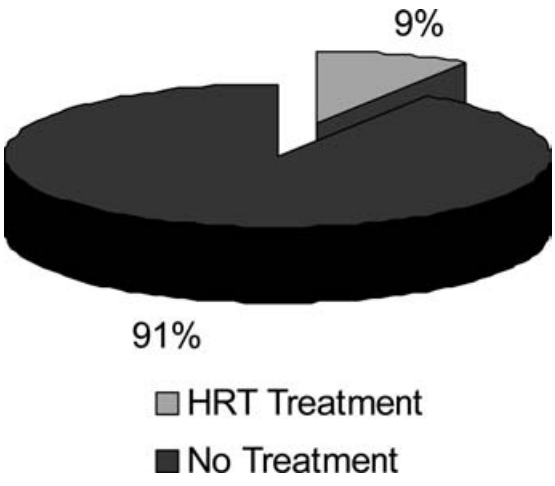

FIG. 1

Percentage of Reinke's oedema patients receiving hormone replacement therapy (HRT).

Discussion

The main conclusion from this prospective case series of 33 cases of Reinke's oedema must be that this pathology does not appear to be related to thyroid function and does not appear to be related to, or affected by, HRT treatment.

As all patients in this study received surgical treatment, patients with mild forms of the disease were not included. We also appreciate that a study assessing the influence of hormonal disturbances on voice production could benefit from more objective outcome measures; a simple questionnaire has its limitations.

The mainstay of therapy for Reinke's oedema remains surgical decompression of the vocal fold contents together with smoking cessation advice and speech therapy.

This study, like previous studies, shows that Reinke's oedema is a condition that occurs predominantly in post-menopausal women[3–6] and that there is a strong association with smoking.

Despite some expert opinion that Reinke's oedema can be as frequent in men, all series found in the literature reported a significantly higher percentage of women than men with the condition. This may reflect the social unacceptability of the resultant voice quality in women. Nevertheless, given the current level of awareness amongst general practitioners of the need to investigate dysphonia, it seems unreasonable to assume that male patients complaining of voice change would be less likely to be investigated.

The incidence of hypothyroidism in this study was low. Hypothyroidism affects 4–10 per cent of women, with the percentage increasing with age.[7] The finding of two women with borderline hypothyroidism in this study is in line with the expected incidence of this condition in this population group and suggests no relationship between thyroid function and Reinke's oedema. This is in keeping with the findings of a number of studies which have failed to demonstrate a relationship between Reinke's oedema and hypothyroidism,[3,8,9] but contradicts others which claim that such a relationship exists.[10]

Recent studies suggest that the larynx is an organ with a plethora of oestrogen and thyroid receptors and is therefore an oestrogen target organ.[11–14] Hormone receptors are found in the nucleus and cytoplasm of cells in the vocal fold, with a statistically significant difference in age and gender distribution.[12] The presence of laryngeal receptors for gonadal steroids supports a role for hormones in laryngeal development and disease.

Other structural differences, such as the distribution of collagen, exist between the male and female larynx, which may contribute to stress or strain performance.[15] In addition, the vocal folds undergo significant sex-specific changes with aging.[16] In the female larynx, both the mucosa and the vocal fold cover thicken with aging. The SLLP loses density as it becomes more oedematous. The intermediate layer of the lamina propria has the tendency to atrophy only in men. The deep

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layer of the lamina propria of the male vocal fold thickens because of increased collagen deposition. The vocalis muscle atrophies in both sexes.

The stratified squamous epithelium of the vocal folds includes three layers: basal, intermediate and superficial. The stratified squamous epithelium undergoes modifications in both structure and function, depending on the hormonal stimulation it receives.[15,17]

Disorders of the female voice occur during menstruation, pregnancy and the menopause and also during some endocrine diseases of the hypophysis, thyroid gland, adrenal glands and ovaries.[10]

Population surveys have shown that many post-menopausal women experience a deepening of voice when compared with pre-menopausal women,[19,20] which confirms that the female voice undergoes changes at the time of menopause which are not seen in men of similar age. Cytological studies have shown that atrophic and dystrophic changes occur in the post-menopausal laryngeal mucosa which has not been treated with HRT.[11]

- **This paper explores a possible role of hormone replacement therapy (HRT) in the pathogenesis of Reinke's oedema by creating a pseudo-hypothyroidism effect and studies why the disease affects a predominantly post-menopausal female population**
- **The study population were 33 patients diagnosed with Reinke's oedema who presented in the out-patient department before or after treatment**
- **There was no evidence to support a relationship between HRT and the pathogenesis of Reinke's oedema**
- **There was also confirmation of previous studies which concluded that thyroid function is not related to the development of Reinke's oedema**

From all the above, it may be reasonable to assume that the atrophic changes of menopause render the larynx susceptible to the chronic 'insult' of smoking, resulting in Reinke's oedema.

Women's vocal quality changes following hormonal treatment for the management of conditions such as endometriosis and hormonal imbalance, as well as following the treatment of post-menopausal women with HRT.[21] Therefore, the larynx may be considered as a secondary sex organ.

It is estimated that up to 30 per cent of all post-menopausal women in Britain receive treatment with HRT.[22] In our study, this figure was nine per cent (3/33 patients). It is therefore unlikely that HRT treatment has any influence on the pathogenesis of the disease. It is probably also reasonable to assume that this study contradicts the theory that HRT treatment implicates indirectly the thyroid gland by increasing T4 requirements.[23]

On the contrary, HRT has been used to forestall menopause-associated voice changes, particularly among professional singers, although these studies lack any objective voice measurements to support this treatment.[11,23]

Further studies will be required to elucidate any possible beneficial effect of HRT in the morbidity of Reinke's oedema.

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