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Research Article

Correlation between Thyroid Ultrasound Findings and Eye Signs in Patients with Hashimoto Thyroiditis

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Abstract

Background: Approximately 25% of patients with Hashimoto thyroiditis (HT) have mild eye signs whilst 3% have typical ophthalmopathy with severe congestive changes, proptosis and eye muscle damage. In Graves ophthalmopathy, there is evidence that the orbital reactions are closely associated with those in the thyroid, either through autoantibody cross-reactivity or by homing of sensitized thyroid lymphocytes to the orbits. The relationship between the thyroidal and orbital tractions in HT is less clear.

Clinical Subjects: We studied 72 patients with HT with (n = 23) and without (n = 49) ophthalmopathy, correlating their real-time thyroid ultrasound findings with the presence of not of ophthalmopathy.

Methods: We have developed a 5-stage classification system for the inflammatory changes seen on thyroid ultrasonography in patients with HT. The early signs are characterised by features of mild inflammation in a normal or slightly enlarged thyroid through to the late stages in which black "holes" are seen in place of the destroyed thyroid tissue, and the gland becomes shrunken, scarred and avascular.

Results: Although we found no significant correlation between thyroid ultrasound stages and the presence or not of ophthalmopathy, patients with more severe ultrasound changes (stages 3 - 5) had a greater prevalence of ophthalmopathy than those early/mild changes (stages 1, 2).

Conclusion: A larger prospective study needs to be carried out to further address this relationship and whether or not the thyroid inflammation and the orbital inflammation occur in parallel, as in Graves disease, or independently. If the latter, it would suggest that HT and the ophthalmopathy are separate autoimmune disorders.

Keywords: *Hashimoto Thyroiditis; Ophthalmopathy; Ultrasonography; Thyroid Autoimmunity*

Introduction

Hashimoto thyroiditis (HT) is a common, organ-specific, autoimmune disorder of the thyroid gland that affects around 8% of adult women and 2% of men. The cytotoxic antibody and sensitized T lymphocyte-mediated autoimmune reactions in HT are usually progressive over months or years leading to hypothyroidism when the thyroid follicular cells have been destroyed. The inflammatory changes in the thyroid can be followed through to the end stage by real-time thyroid ultrasonography [1,2]. Risk factors for HT include: female sex, age, smoking, iodine deficiency and a SNP for the calsequestrin (CASQ1) gene rs3838216 [3]. It is not well recognised that some patients with HT have eye signs, which are usually mild and different from those of Graves ophthalmopathy. Overall, approximately 25% of patients with HT have mild eye signs including: upper eyelid retraction and lag, itchy, gritty and watery eyes and mild eyelid swelling [4-6]. Three % of patients have more severe eye changes similar to those seen in patients with Graves ophthalmopathy namely: chemosis, conjunctival injection, periorbital swelling, proptosis and eye muscle damage [7,8]. Risk factors for ophthalmopathy in patients with HT include smok-

ing, male sex and older age [9]. Thyroid-stimulating hormone-receptor (TSH-R) antibodies are not a risk factor for the development of eye changes in HT as they are not usually detected in these patients [10,11]. Because of their contrasting associations with TSH-R antibodies and different risk factors, the pathogenesis of the eye changes of HT is presumed to be different from that of Graves ophthalmopathy, although this has not been proven.

Antibodies against the eye muscle antigen calsequestrin are detected in a small proportion of patients with HT and eye signs [12] but are probably secondary to eye muscle damage as the protein is intracellular. Antibodies against the orbital fibroblast cell membrane antigen collagen XIII may have a pathogenic role, but this has not been studied in HT. Because the thyroid autoimmune reactions in HT are often extensive and severe, it is possible that the development of ophthalmopathy is a feature of more severe HT, as has been postulated also for Graves ophthalmopathy [13]. An extension of this notion is the possibility that the severity of the inflammation correlates with the existence of mild ophthalmopathy and its severity.

In order to address the relationship between the eye changes in HT and the thyroid immunological reactions, we have developed a 5-stage classification of the thyroid inflammatory changes of HT. In this retrospective study of patients with HT and associated ophthalmopathy, we correlated their real-time thyroid ultrasound findings, quantified as inflammatory stages 1 - 5, with the presence or not of ophthalmopathy and its severity. While we found no close correlation between the ultrasound changes and the presence of eye changes patients with more severe thyroid inflammation were more likely to have ophthalmopathy than those with early changes.

Clinical Subjects and Methods

Clinical subjects

We studied a total of 70 patients with HT; 11 males and 59 females of whom 23; 3 males and 20 females aged 18 - 68 (mean age 47 yr.) had eye signs and 47, 8 males and 39 females aged 17 - 65 (mean age 40 yr.) had no eye signs. Twenty patients had combinations of the following eye symptoms; itchy and/or gritty eyelids, watery eyes and signs; mild eyelid and periorbital puffiness or upper eyelid retraction and lag, which we described as mild ophthalmopathy, i.e. NOSPECS classes [14] 1 or 2 and Clinical Activity Scores (CAS) [15] 1 or 2 and 3 patients had more severe ophthalmopathy with eye muscle dysfunction, chemosis, conjunctival injection and periorbita swelling and exophthalmos. The diagnosis of HT was based on the classical clinical features of a hard-irregular goitre, thyroid tenderness, lymphadenopathy and symptoms of the associated hypothyroidism namely; fatigue, cold intolerance and weight gain and confirmed from thyroid testing, positive serum thyroid peroxidase and thyroglobulin antibodies and inflammatory changes on thyroid ultrasound of the patients were euthyroid and were hypothyroid with elevated TSH and low T4.

Real-time thyroid ultrasonography

The immunological changes observed on real-time thyroid ultrasonography in patients with HT have been classified into 5 stages as follows; Stage 1 is characterised by mild inflammatory changes manifest as small cystic lesions representing the lymphoid nodules and inflammatory infiltrations in normal or slightly enlarged thyroid. In stage 2, the gland is enlarged and the cystic areas are better defined, more frequent and larger; the blood supply to the gland is increased in stages 1 and 2. In stage 3, the thyroid is generally bigger and the signs of inflammation increased with larger inflammatory nodules and the blood supply is now patchy. In stage 4 the gland is becoming avascular and the nodules are replaced by hypoechoic (black) spaces with scar tissue (fibrosis), and there are increased sheets of fibrosis, giving the appearance of pseudo-nodules. In the final stage, the gland is shrunken and scarred with absent blood supply and devoid of thyroid tissue. Examples of the two types of stage 5 changes are shown in figure 1A and 1B.

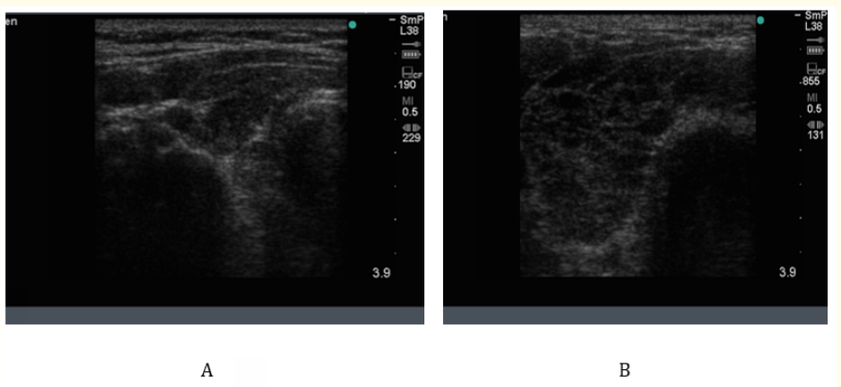

Figure 1: *Thyroid ultrasound findings in 2 patients with different features of Hashimoto Thyroiditis. In (A), the dominant feature is diffuse hypoechoicity, seen as black "holes" indicating the absence of thyroid tissue, some scarring, decreased vascularity and architectural damage in an overall enlarged gland. In (B), the thyroid gland is shrunken, scarred and shrivelled with pseudo nodules and scattered fibrous bands in a small gland; this is the final stage and the patient has no thyroid function.*

Statistics

The correlation between thyroid ultrasound appearances and presence or not of mild ophthalmopathy in patients with HT was analysed statistically using the 2 x 2 chi^2 test. A p-value of < 0.05 was taken as significant.

Results

We addressed the relationship between the presence or not of mild ophthalmopathy and immunological changes on thyroid ultrasonography classified as stages 1 - 5, in patients with HT with and without ophthalmopathy. The results are summarised in figure 1 and 2. The number of patients (n) with or without ophthalmopathy was correlated with their thyroid ultrasound stage (1 - 5), determined by a single observer at the time of their first clinic visit. Of the 23 patients with ophthalmopathy, 5 had stage 1 changes, 7 had stage 2 changes, 2 had stage 3 changes, 5 had stage 4 changes, and 4 had stage 5 changes.

Overall, there was no significant correlation between ultrasound findings, classified as stages 1 - 5 and the presence of ophthalmopathy (Chi^2 test, P = NS). However, As can be seen in figure 2 and 3, there was a tendency for patients with later stages of thyroiditis (stages 3 - 5) to have ophthalmopathy than those with stages 1 and 2.

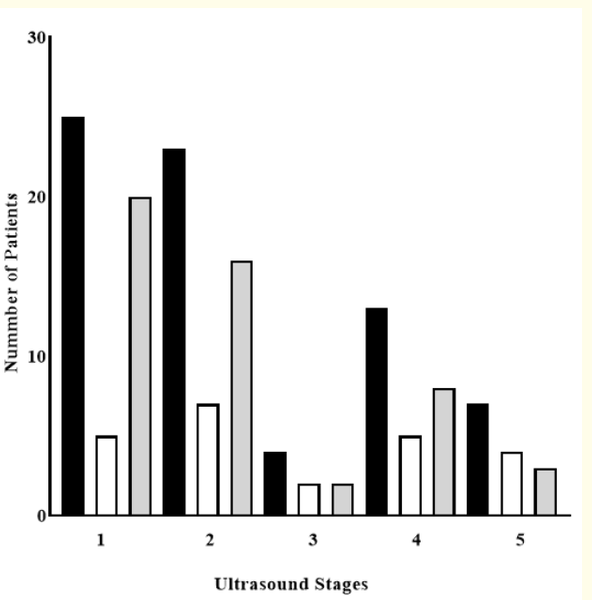

Figure 2: *Correlation between thyroid ultrasound findings measured as inflammatory stages 1 - 5 and the presence of ophthalmopathy in patients with Hashimoto thyroiditis where ■ = total number of patients, □ = patients with ophthalmopathy, and ▢ = patients with no ophthalmopathy*

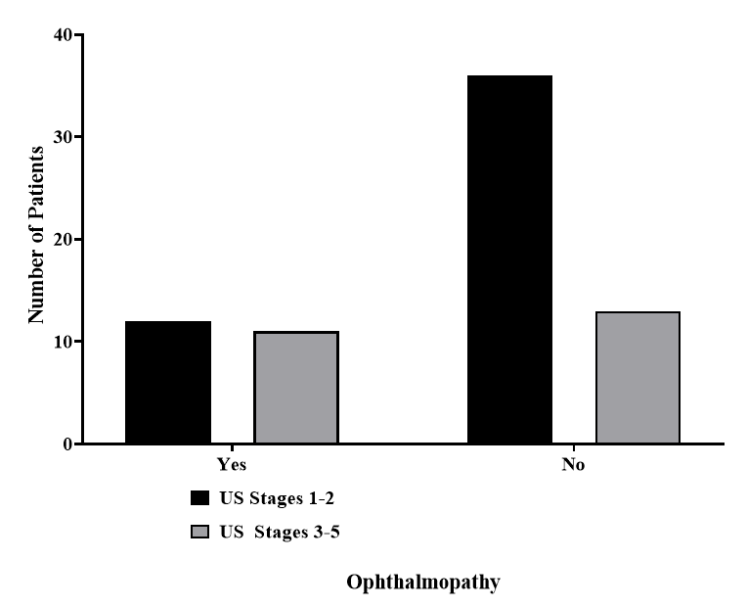

Figure 3: *Correlation between thyroid ultrasound findings, quantified as inflammatory stages 1-5, and the presence of ophthalmopathy in patients with Hashimoto thyroiditis where* ■ *= ultrasound stages 1 and 2 and* □ *= ultrasound stages 3 - 5 in patients with and without ophthalmopathy.*

Finally, there was no significant correlation between the severity of the eye features, measured as Clinical Activity Score (CAS, 0-10) and NOSPECS class and ultrasound stage (results not shown).

Discussion

Approximately 25% of patients with HT have mild eye signs [4-6] and 3% have typical ophthalmopathy with severe congestive changes, proptosis and eye muscle damage [7,8]. In Graves ophthalmopathy, there is evidence that the orbital reactions are closely related to those in the thyroid, possibly through cross-reactive antibodies or by homing of sensitized thyroid T lymphocytes to the orbits [16,17] in both cases leading to complex autoimmune reactions involving many cell types, cytokines, other soluble protein and their receptors. The relationship between the thyroidal and orbital reactions is (in) patients with HT is less clear.

In order to better understand the progressive inflammatory changes of HT, we have developed a new classification system for the inflammatory changes seen in the thyroid on ultrasonography of patients with HT. The early signs are characterised by features of mild inflammation in a normal or slightly enlarged thyroid through to the late stages in which black spaces replace the destroyed thyroid tissue, and the gland becomes shrunken, scarred and avascular.

In this retrospective study of patients with HT and associated mild ophthalmopathy, we correlated their real-time thyroid ultrasound findings, quantified as stages 1 - 5, with the presence and severity of any eye signs. To summarise the main findings; although we found no close correlation between the ultrasound changes and ophthalmopathy, there was a tendency for patients with ophthalmopathy to have more severe changes on ultrasonography (stages 3 - 5) than those with early changes (stages 1, 2).

TSH-R antibodies are not generally detected in patients with what we can call "Hashimoto ophthalmopathy" [10,11] so the pathogenesis of the eye changes of HT is presumed to be different from that of Graves ophthalmopathy. Antibodies against the eye muscle antigen calsequestrin are detected in some patients with HT and eye signs they are probably secondary to eye muscle damage as the protein is intracellular. Antibodies against the orbital fibroblast cell membrane antigen collagen XIII may have a pathogenic role, but this has not been studied in HT. The eye changes of HT do not usually require anti-inflammatory therapy and are relieved by soothing eye drops.

Conclusion

In conclusion, a larger prospective study needs to be carried out to further address this relationship and whether the thyroid reactions and orbital inflammation occur in parallel, as appears to be the case in Graves disease or independently. If the latter, it would suggest that HT and the ophthalmopathy that is sometimes associated are separate disorders.

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