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Review Article

What Does the Use of Radioiodine Treatment of Graves' Hyperthyroidism Tell Us About the pathogenesis of the Associated Ophthalmopathy?

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Abstract

Thyroid-associated ophthalmopathy (TAO) is a complex disease that can lead to major functional, cosmetic and emotional consequences and negatively impact the patient's quality of life. The condition is difficult to treat, partly because the mechanism for the development of ophthalmopathy remains unclear. It is hypothesized that antibodies and sensitized T lymphocytes targeting thyroid antigens cross react with similar proteins in the orbital connective tissues and eye muscles leading to the inflammatory changes that characterize TAO. Most patients with ophthalmopathy develop the eye disorder at about the same time as the hyperthyroidism or soon after the diagnosis, lending support to the cross-reactivity hypothesis.

The treatment of Graves' hyperthyroidism with radioactive iodine (RAI) leads to thyroid inflammation and the release of antibodies against shared antigens that may aggravate existing eye disease. It is estimated that up to 25% of TAO patients may have transient worsening of their eye symptoms post-RAI therapy compared to 15% of patients treated with anti-thyroid medications or surgery. The treatment of TAO remains suboptimal and future studies looking at antigens that play a role in the development and progression of TAO are needed.

Keywords: *Thyroid-Associated Ophthalmopathy (TAO); Graves' Hyperthyroidism; Radioactive Iodine (RAI)*

Introduction

The eye disorder associated with Graves' hyperthyroidism, called Graves' ophthalmopathy (GO), Graves' orbitopathy or, more accurately since it also occurs in some patients with Hashimoto thyroiditis, thyroid-associated ophthalmopathy (TAO), remains a complex and somewhat controversial disease. Severe ophthalmopathy can lead to major functional cosmetic and emotional consequences and poor quality of life, that are difficult to treat.

That the ophthalmopathy is autoimmune is well established and the TSH-Receptor (TSHr) [1] the IgF-1 receptor (IgF-1R) [2] and the skeletal muscle protein calsequestrin (CASQ1) [3,4] have been identified as possible targets of autoantibodies [3,4] and sensitized T lymphocytes [5] in GO. The mechanism for the development of ophthalmopathy in some, but not all, patients with Graves' hyperthyroidism is unclear but most workers favour the hypothesis that antibodies and sensitized T lymphocytes targeting thyroid antigens home to the orbit where they cross react with the same or similar proteins in the orbital connective tissues (OCT) and eye muscles [6-9]. The TSHr is expressed in the orbital pre-adipocytes and fibroblasts [10,11] and there is evidence that the dominant thyroid autoantigens thyroglobulin (Tg) and thyroid peroxidase (TPO) [12,13] and the IgF-1 receptor [13] are also expressed in the orbit.

In addition, a large number of soluble mediators of the autoimmune reaction including; cytokines, lymphokines, homing proteins, immune co-factors and their receptors have been identified to play a role [12,14]. Regardless of the precise mechanisms, the immune reactions lead to the orbital swelling, conjunctival inflammation and eye muscle dysfunction that characterises ophthalmopathy.

Temporal relationship between the hyperthyroidism and ophthalmopathy

In strong support of the cross-reaction hypothesis is the observation that most patients with ophthalmopathy develop the eye disorder at about the same time as the hyperthyroidism or soon after [15,16]; indeed, it is rare to develop ophthalmopathy more than a year after the onset of the hyperthyroidism. It follows therefore that workers who study the nature of the orbital autoimmune reactions in Graves' disease must consider the primary role of the thyroid gland in this, implying that there must be some close link between the autoimmune reactions in the two sites. While it is unclear whether the observed reactions are directly pathogenic in the orbit or just markers of the overall immune reactions there, the observation that the eye signs may worsen after radioiodine (RAI) treatment of the hyperthyroidism in parallel with increasing serum levels of both the antigens and the antibodies, the subject of this mini review, would favour a direct role.

What RAI does in the thyroid

^{131}I enters the thyroid follicular cell under TSH control where it is incorporated into the cellular machinery that leads to the synthesis of the thyroid hormones tetra-iodothyronine (T4) and tri-iodothyrine (T3,) in the same way as native (non-radioactive) iodine. In the gland, beta and gamma radiation from the ^{131}I damages the thyroid follicular cells and the surrounding connective and fatty tissues in a progressive and generalized inflammatory reaction. The thyroid follicular cells are damaged and eventually destroyed, leading to hypothyroidism within 3 - 4 months. In the context of this thyroid inflammation, serum levels of those proteins that are targeted in the thyroid autoimmune reactions of Graves' disease namely, thyroglobulin, the TSH receptor and thyroid peroxidase, are increased [17-19].

Clinical implications of RAI therapy in Graves' disease

Radioiodine (RAI) is an effective treatment for Graves' hyperthyroidism that is used in about 70% of patients with Graves' disease as the first line of management in the US, in about 30% of European patients but in only 15% of patients in Australia and Asia where anti-thyroid medication is routine. These markedly different prevalence's reflect different attitudes towards medical radiation in North America, Europe and Asia, that have little to do with the actual effects and side effects of the treatment. Because RAI is the best modality for definitive therapy of patients with Graves' hyperthyroidism following relapse after 12 - 18 months of anti-thyroid medication, unjustified fear of RAI treatment has important implications in the management of this common disorder worldwide.

According to the cross-reactivity hypothesis, thyroid antibodies, as well as clones of T lymphocytes sensitized to the same antigens, pass (home) to the orbit where they would increase the inflammation in the orbital tissues. As a result, existing ophthalmopathy would be expected to worsen for a few days or weeks following RAI [20-22], but then improve in the longer-term because the thyroid antigen mass – the proteins that drive the inflammatory reaction in the orbit - has been destroyed by the RAI. In further support of this, total thyroidectomy - by removal of (almost) all of the thyroid proteins - has been shown to result in improvement of existing eye disease in patients with GO and its prevention in patients with Graves' hyperthyroidism [23-25].

The early studies that showed an effect of RAI on the eye disease [26,27] are somewhat controversial but, from later studies, it is now generally agreed that in around 25% of Graves' disease patients treated with RAI, existing eye symptoms worsen transiently compared to 15% of patients treated with anti-thyroid medication or by surgery [28-31]. It is very rare for either development of new eye disease, or a flare-up of existing ophthalmopathy, to occur more than 4 - 6 weeks after RAI treatment. The author and his colleagues did publish one case where new ophthalmopathy occurred a few days after RAI in a female patient [32], but we think that the eye disease in that patient was not typical as the eye signs improved very rapidly to near normal over 10 days and she did not have eye muscle swelling or damage. Whilst expected to be rare, the risk of the development of new thyroid ophthalmopathy following RAI can be minimised by rendering the

patients euthyroid with a thionamide before radioiodine, to follow them closely to detect and correct early hypothyroidism or persistent thyrotoxicosis by advising patients not to smoke.

Role of calsequestrin in the pathogenesis of ophthalmopathy and effect of RAI

We have shown that serum autoantibodies against CASQ1 are good markers for the eye muscle component of GO [3,4,33-35]. In addition we have recently demonstrated an association of the CASQ1 gene rs3838216 with Graves' ophthalmopathy and Hashimoto's thyroiditis in patients with thyroid autoimmunity [36,37]. We have also shown that CASQ2, the cardiac muscle equivalent of CASQ1, was expressed 4.1 times more in the thyroid of Graves' patients with ophthalmopathy than in those without eye signs [38] and that this increased expression correlated with reduced levels of the protein in the thyroid gland in patients with GO [39], suggesting that autoimmunity against CASQ1 could play a role in the development of the ophthalmopathy. In a recent study Sun., *et al.* [40] confirmed our findings of an increased prevalence of CASQ1 antibodies in Graves' patients with ophthalmopathy compared to those with no ophthalmopathy, and normal subjects' numbers in Graves' disease patients with ophthalmopathy compared with those without eye signs. Additionally, there is evidence for specific sensitization to thyroid T cells to CASQ1 and changes in T cell subset numbers in patients with GO [41].

Because CASQ1 antibodies are also found in some normal subjects and in patients with various other muscle disorders such as myasthenia Gravis, polymyositis and after severe exercise or muscle trauma (Lahooti Wall., *et al*. unpublished observations) it seems likely that these antibodies are secondary to a T cell reaction against one or more of the thyroid antigens expressed in the orbit or an as yet to be identified cell membrane antigen although a primary role in GO has not been excluded.

Implications for treatment of Graves' ophthalmopathy

Fifty percent of patients with Graves' hyperthyroidism treated with a 12 - 18 months course of anti-thyroid medication relapse and are treated with RAI or surgery. However, as we have seen, RAI can sometimes lead to worsening of existing ophthalmopathy or, rarely, cause it. In the future, it will be possible to prevent ophthalmopathy in patients with Graves' hyperthyroidism. For example, those patients with hyperthyroidism and positive marker auto antibodies shown to be associated with active eye disease, and thus at risk for ophthalmopathy, could be treated with specific monoclonal antibodies without serious side effects. In the meantime, the best we can do is to treat the eye disease as early as possible with anti-inflammatory agents, such as oral or IV steroids. Cytotoxic agents and monoclonal antibodies such as Rituximab, have been used with some success [42,43] but their side effects remind us that the ideal therapy for active ophthalmopathy has yet to be found [13,44].

In patients with serious disease, external radiation or even surgical orbital decompression may be needed. Total thyroidectomy, which removes the bulk of the antigen mass that drives the orbital autoimmune reactions and could be recommended at any stage in the management of Graves' disease, has the added bonus that it treats the associated hyperthyroidism. In summary, RAI is the best treatment for Graves' hyperthyroid patients with no eye signs and total thyroidectomy for those with eye signs, with long term antithyroid medication being reserved for patients who refuse radioiodine as initial therapy or in whom surgery is contraindicated because of poor health.

Conclusions

The observed effects of RAI on some of the key candidate thyroid antigens and their corresponding serum autoantibodies, and including a flare up of the associated orbital reactions in 30% of patients, is convincing evidence to support the cross-reactivity hypothesis [20] for the development of ophthalmopathy in patients with Graves' hyperthyroidism. Moreover, it shows that the reactions in the orbital follow similar reactions in the thyroid gland, implying i) that the process is the same in each organ and ii) directly related but iii) commences in the thyroid. It follows therefore that the mechanism for the development of ophthalmopathy in patients without associated autoimmune thyroid disease so-called euthyroid Graves' disease and in some patients with Hashimoto thyroiditis must have a different pathogenesis.

Future Studies

Serum levels of the TSHR, TPO, Tg and CASQ1 proteins and the corresponding antibodies can be measured in patients with Graves' disease, with and without eye signs, before and after RAI in a multi- centre study. In this way it should be possible to eliminate some of these antigens and focus on those where a relationship between serum levels of the antigen and/or the corresponding antibody and changes in eye signs has been demonstrated. If no correlations are shown one must rethink the cross-reactivity hypothesis and address the possibility that ophthalmopathy is a primary organ specific disorder that is only sometimes associated with thyroid autoimmunity, as the clinical evidence suggests. Of course, this does not mean that we should not search for other possible thyroid and orbital tissue shared and orbital specific, antigens that might turn out to be "the missing link" that explains the development of this complex eye disorder. Finally, it will probably turn out that ophthalmopathy is, like many other autoimmune disorders be T cell driven and involving a large number of other mediators of eye muscle and orbital connective tissue damage.

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