Occurrence of Graves' Orbitopathy and Graves' Hyperthyroidism after a Trauma to the Eye

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What Is Known about This Topic?

- Graves' orbitopathy is believed to be the consequence of autoimmunity against antigens present both in the thyroid and in orbital tissues. Massive release of thyroid antigens causes the appearance or deterioration of Graves' orbitopathy in patients with Graves' hyperthyroidism. A similar release of autoantigens may occur at the eye level resulting in the development of Graves' orbitopathy.

What Does This Case Report Add?

- To our knowledge, this is the first description of a case of de novo appearance of Graves' orbitopathy and then Graves' hyperthyroidism after an eye trauma, possibly reflecting spreading of autoantigens and activation of the immune system against shared orbital and thyroid antigens.

Keywords

Graves' orbitopathy · Graves' disease · Thyroid · Autoimmunity

Abstract

Background: Graves' orbitopathy (GO) is believed to be the consequence of autoimmunity against antigens that are present both in the thyroid and orbital tissues. Massive release of thyroid antigens causes the appearance or deterioration of GO in patients with Graves' hyperthyroidism (GH),

as it occurs following radioiodine treatment. In theory, a similar release of autoantigens may occur at the eye level, for example due to an orbital trauma or surgical manipulation. To our knowledge, this is the first report of a case of de novo appearance of GO and then GH after an eye trauma, possibly reflecting spreading of autoantigens and activation of the immune system against shared orbital and thyroid antigens.

Elena Sabini and Ilaria Ionni contributed equally to this work.

Case Report: An otherwise healthy, 57-year-old man presented 6 months after the appearance of a monolateral right orbitopathy, which occurred 40 days after a trauma in the ipsilateral eye. His thyroid function was normal, with positive serum anti-TSH receptor autoantibodies. The thyroid was normal on ultrasound. A month later he developed hyperthyroidism and orbitopathy in the left eye. **Discussion:** The development of GO after an eye trauma may reflect tissue damage with release of autoantigens and consequent autoimmunity in a predisposed individual (our patient had a familial history of autoimmune thyroid disease). The subsequent development of hyperthyroidism is in keeping with the hypothesis that GH and GO are due to autoimmunity against antigens present both in the thyroid and in orbital tissues.

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Introduction

Graves' orbitopathy (GO) is a disfiguring and disabling disease usually associated with autoimmune thyroid diseases [1]. Thus, ~95% of GO patients have Graves' hyperthyroidism (GH), ~3–4% have autoimmune thyroiditis with hypothyroidism, and ~1–2% have subclinical evidence of thyroid autoimmunity (detectable anti-thyroid autoantibodies) with a normal thyroid function, the former condition known as euthyroid GO [2–4]. The association between GO and thyroid autoimmunity, as well as the influence of the underlying thyroid disease and its treatment on GO [1–4], suggest a close relationship between the thyroid gland and the affected orbital tissues [5]. Thus, most investigators believe that GO is the consequence of autoimmunity against antigens that are present both in the thyroid and in orbital tissues [6]. In this regard, massive release of thyroid antigens is believed to cause the appearance or deterioration of GO in patients with GH, as it occurs following radioiodine treatment, unless a glucocorticoid prophylaxis is given [7, 8]. In theory, a similar release of autoantigen may occur at the eye level, for example due to an orbital trauma or surgical manipulation. In the past, two cases of deterioration of a pre-existing GO after an eye trauma or eye surgery were reported [9, 10]. To our knowledge, this is the first report of a patient with a de novo appearance of GO and then GH after an eye trauma, possibly reflecting spreading of autoantigens and activation of the immune system against shared orbital and thyroid antigens.

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Fig. 1. Photograph of a 57-year-old man with a monolateral, right orbitopathy. Exophthalmos and conjunctival redness in the right eye are quite evident. The left eye is normal.

Case Report

An otherwise healthy, 57-year-old man presented because of a monolateral, right orbitopathy. Approximately 40 days before the appearance of orbitopathy, he was hit in his right eye by a tennis ball while playing on the beach. He had a familial history of thyroid autoimmunity, as his mother had autoimmune thyroiditis. He had no relevant associated diseases and was a smoker (~10 cigarettes/day since he was 17 years old). Approximately 40 days after the eye trauma, he noticed a proptosis in his right eye, because of which his GP ordered thyroid tests that showed a TSH in the lower normal range, with undetectable anti-thyroid autoantibodies, including anti-TSH receptor autoantibodies (TRAb). The thyroid appeared normal on ultrasound. He was given low-dose prednisone (25 mg/day), which was tapered within a few weeks down to withdrawal, with no apparent benefits.

The patient presented approximately 6 months later due to further eye deterioration. Signed informed consent was obtained. At physical examination he had an exophthalmos in his right eye, with eyelid edema and chemosis, and diplopia in the upper and upper-right gaze (Fig. 1). The left eye was apparently normal. He underwent thyroid tests showing a TSH below the lower limit of normal range (0.2 $\mu\text{U/mL}$; normal value [NV] ≥ 0.4), normal FT3 and FT4, undetectable serum autoantibodies against anti-thyroglobulin and anti-thyroxidase, but detectable serum TRAb (3.7 U/L; NV ≤ 1.5). He underwent an ophthalmological evaluation, which suggested the presence of a moderately severe orbitopathy. Thus, exophthalmometry measurements were 23 mm in the right eye and 18 mm in the left eye. He had a lagophthalmos in the right eye, a clinical activity score according to Mourits et al. [11] of 3/7 points (with mild palpebral edema, conjunctival redness, and chemosis, only in the right eye), a normal visual acuity, and a reduction of motility in the upper and lateral gaze in the right eye, with a consequent diplopia in the upper and upper-right gaze. His left eye was apparently normal. An orbital CT scan showed a proptosis in the right eye, with enlargement of the superior, inferior, and medial rectus muscles (Fig. 2). Based on the available data, our diagnosis was "euthyroid, moderately severe, active Graves' orbitopathy," and the patient was offered to undergo intravenous glucocorticoid treatment. Approximately 4 weeks later, when he came back to undergo the scheduled treatment, he complained about tachycardia, fatigue, insomnia, nervousness, increased sweating, and weight loss (approximately 4 kg in 1 month). In addition, he complained about hitching and tearing in his left eye. He underwent thyroid tests, this time showing a suppressed TSH ($<0.001 \mu\text{U/mL}$; NV ≥ 0.4), with

Fig. 2. CT scan of a patient with monolateral, right orbitopathy. Right proptosis as well as enlargement of the right superior, inferior, and medial rectus muscles can be seen.

moderately elevated FT3 (7.3 pg/mL; NV 2.7–5.7) and FT4 (2.3 ng/dL; NV 0.7–1.7). An ophthalmological examination was performed, with a stable picture in the right eye and a mild orbitopathy in the left eye, with 19 mm at exophthalmometry, a clinical activity score of 2/7 points (with mild palpebral edema and conjunctival redness), and normal visual acuity and motility. Based on the findings, the patient was given methimazole, with subsequent control of hyperthyroidism and, as scheduled, intravenous glucocorticoids, with a subsequent improvement of GO in both eyes. Thus, after 6 months, the clinical activity score was 1/3 points in both eyes, and diplopia had improved from inconstant to intermittent, with no changes in exophthalmometry measures.

Discussion

The case we reported suggests a possible cause-effect relationship between eye traumas and the occurrence of GO and GH. The idea is that a trauma may cause a tissue damage, with subsequent spreading of autoantigens, which in a predisposed individual – our patient had a familial history of thyroid autoimmunity – may trigger autoimmunity against these antigens, thereby precipitating GO first and then GH, the latter due to the very high likelihood that the two conditions reflect autoimmunity

against antigens shared by the thyroid and orbital tissues [5, 6].

The possibility that GH and GO have a common pathogenesis is suggested by the very close relationship between the two conditions. Thus, GO is observed mostly in GH patients [3], with a very close temporal relationship between the onset of the thyroid and the eye disease [12–14]. In addition, the severity of GO seems to parallel that of GH, as for example indicated by the relation between thyroid volume and the degree of GO [15]. In support of a relationship between the pathogenetic mechanism of GH and GO, the severity of hyperthyroidism correlates with GO. Thus, GO is more severe in patients with untreated hyperthyroidism [16], and worsening of GO is more common in patients who undergo relapse of hyperthyroidism after withdrawal of anti-thyroid drugs [17].

The concept that spreading of autoantigens due to tissue damage may precipitate autoimmunity against the same antigens is supported by the relationship that exists between radioiodine treatment and the onset or worsening of GO [1, 7, 8]. Thus, randomized clinical trials indicate that treatment of GH with radioiodine can be followed by the de novo appearance or worsening of a pre-existing GO [18–21]. Presumably, the appearance or deterioration of GO reflects the massive release of thyroid antigens that follows radioiodine therapy, with consequent activation or re-activation of the immune system against the same (or similar) antigens expressed by orbital tissues. In support of this hypothesis, radioiodine treatment is followed by an increase in TRAb levels [22], the TSH receptor probably being the most important autoantigen for GH and GO [5].

To our knowledge, there were no previous reports on GO de novo appearance after an insult to the eyes. However, there are two reports of worsening or re-activation of a pre-existing GO after eye trauma or surgery. Thus, in 2003, Wai et al. [9] reported the case of a 63-year-old man with a long-lasting, mild GO who developed a severe eye disease after retrobulbar anesthesia for cataract extraction. In 2015, Papakostas et al. [10] reported the case of a 63-year-old woman who had a significant worsening of a pre-existing GO after a periorbital trauma. Coupled with our observation, these reports support the hypothesis that an eye trauma and the subsequent spreading of autoantigens may be responsible for the de novo appearance or deterioration of GO, which is in line with the autoimmune nature of the eye disease. In our case, the subsequent development of hyperthyroidism is very much in keeping with the hypothesis that GH and GO are due to autoimmunity against autoantigens present both in the

thyroid and in orbital tissues [5, 6]. Of course, we cannot prove that there was a direct cause-effect relationship between the eye trauma and the occurrence of GO and GH in our patient. However, based on the knowledge of the autoimmune nature of GO and of the mechanisms underlying the development of GO in GH patients, we believe that this possibility is very likely, which offers a further little piece of knowledge of the pathogenesis of GO.

Disclosure Statement

The authors have no conflict of interest.

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