**Author’s response to reviews**

**Title:** Exophthalmos in a young woman with no Graves' disease - a case report of IgG4-related orbitopathy

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Dr Guangde Tu
Editor
BMC Ophthalmology

Dear Dr Tu,

We would like to thank for your letter and the possibility to submit our revised manuscript „Exophthalmos in a young woman with no Graves’ disease - A case of IgG4-related orbitopathy” (BOPH-D-17-00382) to BMC Ophthalmology.

We are grateful to the reviewers for their constructive and important comments as well as for the critiques that have helped us to improve our manuscript. We tried to address all of the Reviewers’ questions and comments.
Please find below our point-by-point responses to each of the reviewers’ comments.

Answers to William Robert Nunery, MD, PhD, Reviewer 1

The paper would benefit with a re-write with an English editor. The examples are too numerous to mention, but a sample suggestion for the first paragraph of the abstract might be something like, "Immunoglobulin G4-related disease (IgG4-rd) is characterized by lymphoplasmacytic infiltration and tissue fibrosis. Orbital manifestations of IgG-rd may include unilateral or bilateral proptosis, cicatricial extraocular muscle myopathy, orbital inflammation and pain which may mimic ophthalmic Graves' disease." This type of rewrite should continue throughout the paper.

We have rewritten the paper which has now been edited by a native English speaking colleague. We used the suggested abbreviation IgG4-rd through the manuscript.

The copy provided to me appeared to have previously been edited. While I agree with many of the suggestions of the editing, the additional information pertaining only to Graves' disease is excessive. Text lines 51-94 mostly pertain only to Graves' disease diagnosis and treatment, and detract from the point of the paper, which is to discuss IgG-4 disease. I would keep lines 51 through 58, "The annual incidence of Graves'.... sensation behind the eyes." Lines 59-68 are not additive to IgG-4 discussion.

Yes, the manuscript has been previously edited.

We modified the Background section as suggested:

"The most common orbital disease usually with exophthalmos is Graves’ orbitopathy, which is the extrathyroidal complication of Graves’ thyroid disease [1]. The annual incidence rate of Graves’ orbitopathy has been estimated at 16 cases per 100,000 women and 2.9 cases per 100,000 men in one rural Minnesota community [2]. Graves' orbitopathy usually appears simultaneously with or soon after the development of thyrotoxicosis; however, rarely it may precede hyperthyroidism. The most common clinical features of Graves’ orbitopathy are upper eyelid retraction, oedema, and erythema of the periorbital tissues and conjunctivae, proptosis, dry ocular sensation, photophobia, double vision, and pressure sensation behind the eyes. Beside detailed ophthalmological examination (best-corrected visual acuity, color vision, pupillary examination, ocular motility, Hertel’s exophthalmometry, intraocular pressure, adnexal examination, slit-lamp examination, dilated fundus examination) laboratory parameters that are necessary to confirm the diagnosis include: measurement of serum thyroid stimulating hormone, free thyroxin, and TSH receptor antibody levels. In euthyreoid Graves’ orbitopathy, TSH receptor antibody level is elevated without thyroid function abnormality. The diagnosis of
Graves’ orbitopathy in most patients is obvious; however, exophthalmos can also be present in patients with lymphoproliferative disorders of the orbits, idiopathic orbital inflammatory syndrome, orbital myositis, severe obesity, Cushing’s syndrome, histiocytosis, granulomatosis with polyangitis, and IgG4-related orbitopathy [1, 3, 4]. Orbital magnetic resonance imaging, orbital computed tomography and/or single photon emission computed tomography can help to distinguish between the underlying causes [5, 6, 7, 8]."

The paragraph beginning on line 76, "The diagnosis of Graves’ orbitopathy... distinguish between underlying causes." is germane, but I question the inclusion of myasthenia gravis in the differential. I would rather include granulomatosis with polyangiitis on that list.

We include granulomatosis with polyangiitis on the list and deleted myasthenia gravis:

"The diagnosis of Graves’ orbitopathy in most patients is obvious; however, exophthalmos can also be present in patients with lymphoproliferative disorders of the orbits, idiopathic orbital inflammatory syndrome, orbital myositis, severe obesity, Cushing’s syndrome, histiocytosis, granulomatosis with polyangitis, and IgG4-related orbitopathy [1, 3, 4]. "

Lines 84 to 94, dealing w/ Graves' disease treatment, are not germane and are debatable. This addition does not help the paper, in my opinion.

We deleted section dealing with the treatment of Graves’ disease and related reference as requested.

The brief pathology discussion on lines 103-105 should include the presence of IgG-4+ plasma cells, as well as the description of storiform fibrosis and obliterative phlebitis which were added on lines 115. It might also be noted that storiform fibrosis and obliterative phlebitis are more typical in the systemic pathology, and not always present in the orbital disease.

We modified and completed the brief pathology discussion:

"Features of IgG4-rd include tumor-like swelling of involved organs, lymphoplasmacytic tissue infiltration enriched in IgG4-positive plasma cells, storiform fibrosis and obliterative phlebitis [4, 10, 11]. The number of IgG4-positive plasma cells per high-power field (HPF) that is regarded as consistent with or suggestive of IgG4-rd varies somewhat from tissue to tissue. Generally, the minimum for making the diagnosis for most tissues is from 30 to 50 IgG4-positive cells/HPF. However, in the lacrimal gland, 10 IgG4-positive plasma cells/HPF may be sufficient for the diagnosis [13, 14, 15]. Storiform fibrosis and obliterative phlebitis are more typical of the systemic pathology; however, they are not always present in the orbital disease."
The case presentation (lines 145- 203), I believe, is misplaced in the manuscript. I would rather place this portion of the manuscript immediately following line 82, "... distinguish between underlying causes." After the case presentation, then return to the discussion of the systemic manifestations and descriptions of IgG-4rd.

We modified the structure of the manuscript as requested.

Answers to James Garrity, MD, PhD, Reviewer 2

It appears as though a working (not a final copy) of the manuscript was submitted

Yes, the manuscript has been previously edited.

Line 25: awkward sentence……"to Graves orbitopathy"

We modified the first paragraph of the abstract:

"Background: Immunoglobulin G4-related disease (IgG4-rd) is characterized by lymphoplasmacytic infiltration and tissue fibrosis. Orbital manifestations of IgG4-rd may include unilateral or bilateral proptosis, cicatricial extraocular muscle myopathy, orbital inflammation and pain which may mimic ophthalmic Graves' disease."

Line 29: treated with what?

We completed this sentence:

"She has had bronchial asthma and recurrent skin rashes of unknown aetiology for the last ten years and was treated for dacryoadenitis with steroid containing eye drops five years ago."

Line 35: you mean no presence of TSH receptor antibodies?

We corrected this sentence:

"Thyroid function tests were in the normal range and no thyroid stimulating hormone (TSH) receptor autoantibodies were present."
Line 68: what does the detailed eye examination look for?

We completed this section:

"Beside detailed ophthalmological examination (best-corrected visual acuity, color vision, pupillary examination, ocular motility, Hertel’s exophthalmometry, intraocular pressure, adnexal examination, slit-lamp examination, dilated fundus examination) laboratory parameters that are necessary to confirm the diagnosis include: measurement of serum thyroid stimulating hormone, free thyroxin, and TSH receptor antibody levels."

Line 82: might state how imaging helps distinguish

The detailed description of the differences in orbital images would substantially lengthen the manuscript. Instead, new references were added here:

"Orbital magnetic resonance imaging, orbital computed tomography and/or single photon emission computed tomography can help to distinguish between the underlying causes [5, 6, 7, 8]."


Lines 89-92: what is the evidence to support these statements?

We shortened the manuscript as requested by Reviewer 1, and deleted the section dealing with the treatment of Graves’ orbitopathy.

For your information, the references supporting the deleted statements (line 89-92 in the „original” manuscript):

Marcocci C, Bartalena L, Bogazzi F, Bruno-Bossio G, Lepri A, Pinchera A. Orbital radiotherapy combined with high dose systemic glucocorticoids for Graves’ ophthalmopathy is more effective


We inserted the suggested reference:

" Orbital involvement most frequently includes the lacrimal glands and extraocular muscles, however, infraorbital and supraorbital nerve enlargement may also be detected [12]."


We inserted the suggested reference:

"In those who are resistant to glucocorticoids, or have side effects or contraindications to glucocorticoid therapy, rituximab is another therapeutic option [9]."

Line 158: dacryoadenitis. This is not a radiographic diagnosis. This condition does not usually respond to steroid drops

Retrospective data from the medical records were the source. We agree that a cause and effect relationship is not likely. We corrected this part of the manuscript:

„Dacryoadenitis was diagnosed by ophthalmological examination and MRI in 2009 (Figure 2, A).”

Line 167: don't need to specify details of the Hertel

We deleted details of the Hertel measurement:

"Propotosis values (measured by Hertel’s exophthalmometer) were 24 mm on the right side, and 21 mm on the left side."

Line 176: what are the typical features?

We completed this section:

"Orbital MRI showed enlarged lateral and superior rectus muscles, and eyelid oedema and swollen lacrimal gland in both orbits while the typical MRI features of Graves’ orbitopathy (proptosis, enlarged extraocular muscles, most frequently the inferior and medial rectuses, excessive amount of orbital connective tissue) were missing (Figure 2, B, C).”

Line 181: glands? Both sides biopsied?

This sentence has now been modified accordingly:

"Histological examination of the right lacrimal gland confirmed the diagnosis of Ig4-related orbitopathy, with both CD138 (the unique cell surface marker of plasma cells) and IgG4 immunohistochemical stainings showing plasmacytic infiltration in the same localisation (Figure 3), and excluding other IgG4 positive conditions thereby confirming the diagnosis of IgG4-related orbitopathy.”

Line 188: what is a skin rush?

We corrected this error:
"Placed on oral corticosteroid administration (methylprednisolone, 16 mg daily) a rapid improvement in both the eye symptoms and skin rashes was observed within a few days (Figure 1)."

Line 196: symptoms
We corrected the error:
"Her skin symptoms are currently under control with glucocorticoid-containing ointments.”

Line 225: the reference describing bone destruction has one case and this one case had saddle nose deformity. It is well known that granulomatosis with polyangiitis can destroy bone, give a saddle nose and also stain positively for IgG4. Bone destruction would make this reviewer think of a disease other than IgG4
We deleted this questionable section from the manuscript.

We inserted this reference:
"IgG4-related orbitopathy may easily be mistaken for Graves’ orbitopathy [24]”

We hope that the changes have improved the quality of our manuscript and the current version reaches the high standards of BMC Ophthalmology.

Sincerely,

Annamaria Erdei, MD