OCULAR ASPECTS OF ENDOCRINE EXOPHTHALMOS*

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UNDER the heading "endocrine exophthalmos" we may consider on the one hand thyrotoxic exophthalmos and on the other the condition which has been designated exophthalmic ophthalmoplegia, malignant exophthalmos, thyrotropic exophthalmos, and also as a hyperophthalmopathic form of Graves's disease (Means, 1945).

As Wybar (1956) has emphasized, the separation of endocrine exophthalmos into the thyrotoxic form and the malignant or oedematous type is a useful clinical division, since "they undoubtedly represent separate phases of the condition".

Can we then, as clinicians, distinguish between the exophthalmos of acute thyrotoxicosis and that which is potentially "malignant" from the ophthalmic point of view? I think, like Mulvany (1944) and other authors, that there is no doubt that we can, and that from the clinical point of view, from the point of view of the patient, it is of the utmost importance that we should try to do so.

Diagnostic Ocular Signs

(a) *Of Graves's Disease.*—In acute thyrotoxicosis the most obvious ocular sign is the lid retraction which varies from day to day. The exophthalmos is often at first more apparent than real and when more advanced is due to "spasm of the anterior orbital unstriated musculature acting in the presence of atonic external ocular muscles", the weakness of the muscles being in part due to the thyrotoxic myasthenia and responding to prostigmine in the early stages (Mulvany, 1944). When the exophthalmos is marked, although the levator may be affected it is never involved without marked impairment of convergence. To these signs we must add the ease with which the eye can be compressed into the orbit.

(b) *Of Malignant or Oedematous Exophthalmos.*—In malignant or oedematous exophthalmos, on the other hand, lid retraction is never evident without impairment of upward movement of the eye, nor does it exhibit the great variability from day to day that is so characteristic of acute thyrotoxicosis.

As the condition progresses, the oedema first appears, as Mulvany has emphasized, as a glistening of the bulbar conjunctiva over the insertion of the recti muscles, due to interference with venous drainage through the anterior

* Read at the combined meeting of the Society of British Neurological Surgeons and the 36th Annual Meeting of the Irish Ophthalmological Society in Dublin, May 16–18, 1957.

ciliary veins draining into the swollen muscles. Later still, we have chemosis, congestion, and puffiness of the soft tissues around the eye. The oedema of the lids is often the first obvious sign because of the laxity of the soft tissues, but I have never seen it in the absence of impairment of upward movement of the eye.

In contrast to the exophthalmos of acute thyrotoxicosis the eye is not readily compressed into the orbit.

The difference in compressibility in the two types of endocrine exophthalmos can now be more accurately assessed with the aid of the orbitotonometer (Copper, 1948).

These features have all been clearly described by Mulvany and other authors but bear, I think, re-emphasis. There should, therefore, be little difficulty in recognizing, from the ocular signs, that an exophthalmos is oedematous or malignant in nature.

Classification of Malignant or Oedematous Exophthalmos

Mann (1946) proposed a clinical classification based initially on a report of eighteen cases and later amplified by a study of a further nineteen cases (Mann, 1951). These 37 cases fell into three groups:

(i) Those with evidence of primary thyroxine deficiency—with associated excess secretion of pituitary thyrotropic hormone.

(ii) Those in which there were initial symptoms of hyperthyroidism followed by spontaneous thyroid failure or failure following thyroidectomy, with an associated excess of pituitary thyrotropic hormone.

(iii) Those in which excess of pituitary thyrotropic hormone and thyroxine appeared to arise spontaneously.

To these three groups we may add a fourth:

(iv) Euthyroid cases, in which there is no evidence of thyroid dysfunction.

We now know that the problem of malignant exophthalmos involves more than simply a balance between the thyroid and the thyrotropic hormone of the pituitary, and it may well be that malignant exophthalmos is due to some still unknown hormone of the pituitary.

Whatever the cause, the clinical grouping of cases remains unaffected. All these patients present a problem requiring the combined judgement of the physician, surgeon, neuro-surgeon, and ophthalmologist.

Unusual Ocular Aspects of Endocrine Exophthalmos

There are two uncommon aspects to which I should like to make special reference. The first is the type of case in which the exophthalmos may remain unilateral over a long period and in which the diagnostic difficulty lies in deciding whether the case is one of orbital tumour or endocrine exophthalmos. The second is the occurrence of visual field defects in cases of malignant exophthalmos, likewise raising a suspicion of orbital tumour.

(1) Unilateral Exophthalmos.—These cases, although relatively uncommon, present a problem in diagnosis and unnecessary exploration of the orbit may be carried out for suspected tumour. This possibility should be borne in mind in all cases of unilateral proptosis exhibiting slight lid retraction or pseudoptosis (from puffiness of the upper lid), impairment of upward movement, a straightforward proptosis—the difficulty in compression being out of proportion to the degree of proptosis (in the early stages), and absence of any evidence of a soft tissue or other shadow on *x*-ray examination of the orbit.

Hermann (1952) reported such a case in a male aged 63 years, with no symptoms suggestive of thyroid dysfunction, proptosis of the left eye, chemosis, and practically complete absence of upward and outward movement.

X-rays of the skull, sinuses, and optic foramina were negative. “The strictly unilateral proptosis without oedema of the lids suggested the presence of an orbital tumour, although the unusual degree of ophthalmoplegia in the presence of only moderate proptosis raised the possibility of exophthalmic ophthalmoplegia which had so far remained unilateral.”

Orbital decompression did not reveal the presence of a tumour. The orbital fat was unusually firm and tense, and the muscles appeared unduly bulky. Histological examination of a portion of muscle revealed lymphocytic infiltration with surrounding glandular degeneration of the muscle fibres. At the end of the operation a tarsorrhaphy was carried out.

About 11 months later, the right eye started to protrude. The exophthalmometer readings were 23 mm. in the right orbit, and 15 mm. in the left. *X*-ray treatment of the pituitary resulted in practically complete disappearance of the exophthalmos 2 weeks after completion of treatment, although a slight defect of upward movement and diplopia were still present.

The following two cases which have been under my care are also of interest:

Case 1, a woman aged 49, first examined on January 17, 1956, gave a history of watering of the right eye for 5 months, followed 2 months later by diplopia which was most marked in the mornings and chiefly occurred on looking upwards. At the same time, she noticed some swelling around the eye with protrusion of the globe. Examination showed defective upward movement of the right eye, some retraction of the right upper lid and 4 mm. of proptosis.

The visual acuity was normal in both eyes and the fundi were normal. The blood sedimentation rate was 2 mm./hr. The Wassermann reaction was negative and *x* rays of the orbits and skull showed no abnormality. The history revealed no significant degree of thyrotoxicosis apart from the fact that she was intolerant of heat.

By March 20, 1956, she had developed slight ptosis of the right upper lid and there was evident peri-orbital oedema in addition to the exophthalmos, and also slight chemosis. The blood-pressure was normal and the pulse rate 80. The thyroid gland showed moderate palpable enlargement of the right lobe inferiorly, but no bruit could be detected over it. A radio-active iodine test of thyroid function showed a rather low total excretion of 32.2 per cent., but a normal excretion curve of 6.1, the figures indicating an absence of any peripheral hyper-metabolism.

A biopsy of the right lateral rectus muscle showed some collagenous replacement of muscle fibres with slight cellular reaction.

Arrangements were made for her to have unilateral irradiation of the retro-ocular tissues on the right side, excluding if possible any pituitary irradiation, and this was begun May 1, 1956. X-ray therapy was confined to the right lateral field, avoiding irradiation of the pituitary, the patient receiving 3,000 r in 3 weeks. (A field of 4×3 cm. was used and no part of the pituitary fossa was included).

Fig. 1 was taken on April 21, 1956, before the irradiation of the orbit was started.

FIG. 1.—Case 1 before orbital irradiation.

When this patient was last examined on February 21, 1957, the proptosis of the right eye was only 0.5 mm. more than that of the left, but there was still slight impairment of upward movement. She said, however, that 4 days before being asked to report for further examination the lids of the left eye had become "puffy" (Fig. 2).

FIG. 2.—Case 1 after orbital irradiation.

In this case the ocular signs have remained unilateral for over a year.

Case 2, a man aged 58 years, first examined on June 6, 1952, gave a history of proptosis of the left eye, commencing 6 weeks previously. The visual acuity and fundi were normal. There was some chemosis of the conjunctiva with 3 mm. of proptosis of the left eye. There was no evidence of hyperthyroidism. X rays of the skull and orbits were negative. He was treated with 2 gr. thyroid daily, because of evidence of "thyrotropic exophthalmos".

In January, 1953, the condition was unchanged, and the dose of thyroid was increased to 3 gr. daily.

In April, 1953, the proptosis was much worse, having increased by 2–3 mm.; he was admitted to hospital and while in the ward the chemosis became so marked that it overlapped the lower lid.

X-ray therapy of the left orbit was commenced on May 28, 1953, the posterior limit of the field extending to the region of the anterior clinoid processes: surface dose, 3,250 r. This was followed by an increase of the oedema during the first few days, after which there was rapid improvement, the chemosis and the oedema of the lids disappearing completely. On September 29, 1953, the movements of the eye were normal and there was only very slight exophthalmos. By February 27, 1954, no difference could be detected between the two eyes and when he was last seen in February, 1957, the condition was unchanged.

In this patient the condition has remained unilateral for nearly 5 years.

(2) **Field Defects in Malignant Exophthalmos.**—Although Naffziger (1933) reported generalized contraction of the fields of vision in two cases of malignant exophthalmos, and loss of the inferior half of the field in another, such cases are very rarely described in the literature.

Igersheimer (1955) reported six cases and Hedges and Scheie (1955) six cases in which defects could be demonstrated in the central fields, indicating involvement of the optic nerve. Of the cases described by Hedges and Scheie (1955), three showed peri-central scotomata, and three showed nerve-fibre bundle defects. All had had hyperthyroidism at some time, although when the field defects occurred, only two were moderately thyrotoxic, two were mildly toxic or in remission, and two were euthyroid.

Naffziger assumed that circulatory impairment in the optic nerves accounted for the defects, since prompt restoration of vision followed when the pressure was relieved by decompression of the orbit. Our experience confirms this, and in this respect the following two cases are of interest:

Case 3, a man aged 54, first seen on March 24, 1954, exhibited definite signs of hyperthyroidism with a moderate degree of exophthalmos. On October 25, 1954, a sub-total thyroidectomy was performed. Early in 1955, signs of ophthalmoplegia became very evident, and the patient was treated with thyroid 2 gr. daily. He developed swelling of the lids, chemosis, and marked interference with all ocular movements. Intravenous ACTH produced some lessening in the degree of exophthalmos. In June, 1955, the proptosis was still increasing and the patient complained of inability to read.

When I first examined this patient on July 30, 1955, the visual acuity in the right eye was 6/9 partly and J. 4, and in the left eye 6/36 partly and J. 20. Examination of the visual fields revealed a central scotoma in both eyes (Fig. 3).

FIG. 3.—Case 3, visual fields on July 30, 1955.

On September 14, 1955, it was apparent that the central scotomata were extending with increasing involvement of macular vision in both eyes (Fig. 4). The visual acuity was 6/9 partly in the right eye and 1/60 in the left eye.

FIG. 4.—Case 3, visual fields on September 14, 1955, before operation.

A bilateral orbital decompression was performed on September 22, 1955. On October 5, 13 days after the operation, the charts of the visual fields (Fig. 5) illustrate the dramatic effect of the relief of pressure upon the optic nerves. The visual acuity had improved to 6/9 and J in the right eye and 5/60 in the left.

FIG. 5.—Case 3, visual fields on October 5, 1955, after orbital decompression.

Case 4, a woman aged 39, was treated in July, 1955, with thiouracil for early thyrotoxic symptoms, and complained 2 months later of difficulty in focusing the eyes and of diplopia in the mornings. In October, 1955, the visual acuity was 6/9 and 6/6. By December, 1955, she had developed marked proptosis, masked by a tremendously tense oedema of the orbit and eyelids. There was marked limitation of abduction in each eye and of upward movements. The optic discs were normal but the visual acuity had fallen to 2/36 in the right eye and 6/60 in the left. Examination of the visual fields revealed a dense central scotoma in each eye.

Treatment was instituted with intravenous ACTH followed by intramuscular injections of cortisone and ACTH gel. A small dose of radio-active iodine was also given, the patient having been found to be only moderately thyrotoxic. Although the oedema appeared to lessen immediately after the start of treatment, there was no true improvement until April, 1956, when the visual acuity recovered to 6/60 and 6/24. A slow and continuous improvement in vision followed. By July, 1956, the visual acuity was 6/24 and 6/9 and in January, 1957, by which time no field defect could be demonstrated, it was 6/6 and 6/5.

Summary

(1) It is possible from the ocular signs alone to differentiate between the exophthalmos of acute thyrotoxicosis and malignant or oedematous exophthalmos.

(2) The ocular signs in malignant exophthalmos may remain completely unilateral over a number of years.

(3) In rare cases the oedema and infiltration of the orbital tissue in malignant exophthalmos may result in scotomatous defects in the visual fields.

(4) While malignant exophthalmos appears to be a self-limiting disease, irradiation or decompression of the orbit is indicated if the exophthalmos becomes so severe as to endanger visual function.

(5) Irradiation of the orbit seems to be an effective method of treatment, in that it appears to cause a regression of the exophthalmos and thus renders decompression of the orbit unnecessary except in very severe cases or those which do not respond to such treatment.

I am indebted to Professor Riddell and to Dr. R. W. Harrington for permission to quote the findings in Case 4.

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