Heterogeneity of failure of visual acuity in Graves' disease

Y. SACHDEV
M.D., D.C.H.

J. C. CHATTERJI
F.R.C.P.

R. C. SHARMA
M.S.(Ophth.), D.O.

*Endocrine Unit, Department of Medicine and Department of Ophthalmology,
Army Hospital, New Delhi—110,010, India*

Summary

The eye manifestations of Graves' disease are usually mild and self-limiting. Occasionally they follow a progressive course leading to visual loss and total blindness. The ocular manifestations bear no relationship to the metabolic state and may appear before, during or after onset of thyrotoxicosis. Characteristically they become evident at about the time of onset of hypermetabolism. Various factors responsible for the failure of visual acuity are discussed with case illustrations.

Introduction

The eye manifestations of Graves' disease are defined in 2 distinct categories: mild or non-infiltrative and severe or infiltrative (Werner, 1961). In the non-infiltrative variety, the common eye changes are prominent staring eyes, proptosis, wide palpebral fissure and lid retraction; while the infiltrative type is characterized by excessive lacrimation, grittiness, chemosis, decreased resilience of eye balls, ophthalmoplegias and fundal changes. Sudden or progressive visual failure due to corneal ulceration, corneal oedema and infiltration, papilloedema and optic atrophy may also be seen. Such cases are rare and usually the ophthalmic manifestations of Graves' disease are a self-limiting process (Brain, 1959).

Clinical features

For the purpose of this article, the clinical cases have been classified into 3 groups: where visual failure was due to – oedema and infiltration, A; involvement of the optic nerve, B; a combination of factors, C.

The clinical profile of 14 patients is given in Table 1.

Correspondence: Col. Y. Sachdev, Endocrine Unit and Radioimmunoassay Research Laboratories, Army Hospital, New Delhi—110,010, India.

Discussion

Exophthalmos goitre was first described by Guiseppe Flajani in 1802, but his description was considered too meagre and inaccurate to merit a serious consideration (Leading Article, 1968). In 1825, the descriptions of 8 cases of exophthalmic goitre were found among the posthumous writings of Caleb Hillier Parry. Graves described it in 1835 while Basedow described its ophthalmic features in 1840 (Leading Article, 1968). Many terms (progressive exophthalmos, infiltrative ophthalmopathy, dysthyroid eye disease, thyrotoxic exophthalmos, malignant exophthalmos, exophthalmic ophthalmoplegia) have been proposed to describe the infiltrative type of ophthalmopathies associated with Graves' disease (Havard, 1972), but most of these do not signify the true nature of the underlying pathology (Taylor, 1960). The term 'congestive ophthalmopathy' is preferred as the lids and conjunctivae are invariably congested and oedema is a frequent feature. The American Thyroid Association (Werner, 1969) have adopted a classification where the 'mild' end of the spectrum is represented by class 1 and the 'severe' end by classes 2–6. Since eye changes may persist after the disease process has subsided, the terms 'active' and 'inactive' are added.

The clinical impression which persisted for over a century was that the ocular manifestations are of purely hyperthyroid origin and occur only with Graves' disease. Over the last 2 decades, however, clinical and experimental studies have shown that the progressive eye changes can appear in euthyroid and hypothyroid state; and may even begin before there is any evidence of thyroid dysfunction (Werner and Ingbar, 1971). This is supported by the authors' experience. Most of their patients were either euthyroid or under treatment for hyperthyroidism while others were frankly hypothyroid. The rate of control of the hyperthyroid state rather than

TABLE 1. Clinical profile

Serial no.	Sex (age, in years)	Diagnosis	Eye manifestations	Treatment	Follow-up
A. VISUAL FAILURE DUE TO CORNEAL OEDEMA AND INFILTRATION					
1.	F (33)	Graves' disease	Gross exophthalmos, lid lag, exposure keratitis, visual acuity 6/6 bilaterally	Partial thyroidectomy	(a) Three days after thyroidectomy gross conjunctival oedema developed, vision reduced to 6/60 bilaterally. (b) Bilateral tarsorrhaphy, oral prednisone (120 mg daily), frusemide, carbimazole and thyroxine. Partial improvement. (c) One month later, bilateral orbital decompression; azathioprine in place of steroids. (d) Vision gradually improved to 6/9 (R), 6/18 (L). Cornea cleared up. Other eye signs persisted.
2.	F (44)	Primary thyrotoxicosis	Bilateral exophthalmos, gross lagophthalmos, chemosis, conjunctival prolapse, diplopia, vision 6/12 (R), 6/18 (L)	Carbimazole + thyroxine	(a) Euthyroid after 8 months' therapy, no improvement in eye signs. (b) Bilateral orbital decompression. Vision gradually improved (6/9 bilaterally). (c) Four years later developed frank hypothyroid state and eye signs deteriorated; bilateral exposure keratitis; corneal ulceration; corneal dystrophy. Vision 6/60 bilaterally. (d) Transient relief from oral frusemide, methyl cellulose eye drops, and chloromycetin eye ointment. (e) Bilateral tarsorrhaphy. (f) Corneal ulceration gradually cleared. Vision improved to 6/9 bilaterally.
3.	F (29)	Graves' disease	Unilateral exophthalmos (L)	Partial thyroidectomy	(a) Soon after operation, worsening of exophthalmos resulted with convergent squint, diplopia, ophthalmoplegia and vision reduced to 6/36 (R), 6/60 (L). (b) Bilateral orbital decompression leading to slight improvement. (c) Two years later, hypothyroid state was observed with gross bilateral exophthalmos, lagophthalmos, extensive ophthalmoplegia and punctate keratitis. Vision reduced to 6/60 (R), 6/60 (L). (d) Tarsorrhaphy, muscle resections and myectomies giving (e) partial relief in eye movements and gradual improvements in vision 6/12 (R), 6/18 (L).

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TABLE 1. *continued*

Serial no.	Sex (age, in years)	Diagnosis	Eye manifestations	Treatment	Follow-up
4.	F (42)	Graves' disease	Bilateral exophthalmos, lid retraction, superficial keratitis, weak convergence, vision 6/18 (R), 6/9 (L). Fields and fundi normal	Carbimazole + thyroxine	(a) Eye signs unabated despite euthyroid state. (b) Bilateral tarsorrhaphy, right orbital decompression. Not much visual improvement. (c) Four years later thyrotoxic state relapsed preceded by complete visual failure in right eye. (d) ¹³¹ I therapy. Tarsorrhaphy extended further on the right eye. Still no improvement and virtually blind in right eye; 6/9 (L). Fundi normal.
5.	M (32)	Graves' disease	Bilateral exophthalmos, lid retraction (R); vision 6/12 (R), 6/6 (L)	(a) Carbimazole + propranolol (b) Carbimazole + thyroxine 3 months later	Three months after initiation of treatment gross conjunctival oedema developed. Vision reduced to 6/36 bilaterally. Oral and local steroid therapy + frusemide, carbimazole and thyroxine—gradual improvement.
6.	M (39)	Primary thyrotoxicosis	Bilateral exophthalmos. Bilateral lid lag, superficial punctate keratitis L > R. Vision 6/6 bilaterally	Carbimazole	Euthyroid after 6 months; eye signs aggravated. Exposure keratitis increased. Vision reduced to 6/36 bilaterally. Bilateral tarsorrhaphy. Vision improved gradually to 6/12 bilaterally.
7.	F (60)	Diffuse toxic goitre	Bilateral lid lag, corneal opacities, and restriction of movements in dextro-elevation and dextro-depression (R). Visual acuity 6/12 bilaterally	(a) Carbimazole. (b) 6 weeks later carbimazole + thyroxine	Euthyroid after 6 months of treatment. Eye signs deteriorated requiring bilateral tarsorrhaphy and appropriate muscle resection.
8.	M (57)	Graves' disease	Bilateral exophthalmos, lagophthalmos	B. VISUAL FAILURE DUE TO OPTIC NERVE INVOLVEMENT Carbimazole for 5 months Clinically euthyroid but (a) Severe diplopia. Fast deteriorating vision (complete failure (R), 5/60 (L)). Severe conjunctival oedema. Complete extraocular paralysis with eye globes fixed in an upward and inward position. (b) Gross constriction, left vision field. Right field could not be plotted. (c) Emergency bilateral orbital decompression resulting in immediate reduction in papilloedema. (d) Oral frusemide and prednisone (120 mg daily) improved vision to 6/36 (L) and less hazy (R). (e) Conjunctival flaps upturned. Muscle resections and myectomies. (f) No improvement in ophthalmoplegia. Right lens completely 'frosted'. Left cataract removed.	

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TABLE 1. *continued*

Serial no.	Sex (age, in years)	Diagnosis	Eye manifestations	Treatment	Follow-up
9.	F (44)	Graves' disease	Proptosis; bilateral lid retraction	Partial thyroidectomy	(a) Blurred vision one month post-op., visual acuity reduced to 6/60 (R), 6/36 (L). Periorbital oedema, restricted upward and outward movement, central scotoma, bilateral incongruous quadrantic hemianopia and optic atrophy. (b) Oral prednisone 120 mg daily. No improvement. (c) Bilateral orbital decompression. Vision improved to 6/18 (R), 6/12 (L).
10.	F (29)	Graves' disease (treated)	Fast deteriorating visual failure, 6/60 (R), 6/36 (L)	Euthyroid; no active treatment	Gradual development of (a) Bilateral ophthalmoplegia: overaction of inferior and internal rectus muscles. Marked constriction of visual fields. Frank optic atrophy (L). Pale optic disc (R). (b) Bilateral orbital decompression. Oral prednisone 120 mg daily for 7 days. (c) Gradual improvement of bilateral visual acuity to 6/6.
C. VISUAL FAILURE DUE TO COMBINATION OF FACTORS					
11.	F (42)	Graves' disease (on carbimazole + thyroxine)	(a) Progressive visual loss 6/24 (R). (b) Bilateral exophthalmos and overactivity of inferior rectus. Punctate keratitis. Corneal ulceration. Macular oedema	(a) Prednisone 120 mg daily for 7 days. (b) Bilateral orbital decompression.	(a) Steroid therapy: abatement of eye signs; no improvement of visual acuity. (b) Decompression: bilateral vision improved to 6/12. Exophthalmos and inferior rectus muscle overaction unabated.
12.	F (34)	Recurrent thyrotoxicosis (carbimazole therapy)	Necrotizing exophthalmos, logophthalmos, corneal ulceration, bilateral convergent squint. Visual acuity reduced to 6/24 (R), 6/18 (L). Ill-defined optic discs, and engorged veins	Partial thyroidectomy	(a) One week post-op. deterioration of eye signs, and gross bilateral papilloedema. Complete ophthalmoplegia. Vision reduced to 6/60 (R), 6/36 (L). (b) Bilateral tarsorrhaphy and orbital decompression. (c) Gradual improvement of vision over following 6 weeks; limitation of movements and diplopia persisting.
13.	F (59)	Graves' disease (treated with ¹³¹ I). Clinically euthyroid on carbimazole maintenance dose	Three months after ¹³¹ I therapy, developed painful swollen eyes with gross exophthalmos, chemosis, oedematous ulcerated conjunctival folds, hazy cornea, impaired upward movements, and blurred optic discs, vision reduced to finger counting both eyes	(a) Bilateral tarsorrhaphy. (b) Oral diuretics and steroids. (c) Thyroxine combined with carbimazole	Vision gradually improved to 6/9 bilaterally.
14.	F (32)	Graves' disease (operation)	One month post-op. developed exophthalmos, chemosis, corneal ulceration, ophthalmoplegia, concentric visual fields, bilateral papilloedema; bilateral vision reduced to 6/60.	(a) Bilateral orbital decompression. (b) Prednisone 120 mg daily	(a) Slight improvement in one eye. (b) One year later thyrotoxic state recurred. Treatment with ¹³¹ I resulted in hypothyroidism. (c) Visual acuity deteriorated bilaterally. Fundoscopy showed optic atrophy. (d) Corrected to euthyroid state with chemotherapy. No improvement of vision.

development of hypothyroidism may be the significant factor. Thus, rapid treatment tends to worsen the ocular manifestations (Aranow and Day, 1965). In some patients, the eye changes were aggravated by thyroid surgery although no definite time relationship was noticed. The incidence of progressive eye changes following subtotal thyroidectomy has been reported as 3 to 7% while following radioiodine therapy it is said to be approximately 5% (Sloan, 1951; Hamilton *et al.*, 1967). Zimmerman (1929) and Thomas and Woods (1936) have described many cases with progressive ocular changes which were initiated by partial thyroidectomy.

The course of exophthalmos and other eye changes is variable and unpredictable (Havard, 1972). In most of the patients it does not progress and behaves as a self-limiting process. What heralds an end is not known. Sometimes it may take years to appear and stay static for prolonged periods or progress haltingly. Hales and Rundle (1960) found progressive exophthalmos in only 24 out of 104 patients followed-up over a period of 15 years.

Visual failure was the result of corneal dystrophy in 7 of 14 patients with Graves' disease. Two patients had aggravation of ocular manifestations soon after partial thyroidectomy. In the other 5, although the euthyroid status was achieved easily with carbimazole, propranolol and thyroxine, the eye manifestations remained unabated and required surgical intervention in the form of bilateral decompression and tarsorrhaphy. The improvement in the eye signs was slow, incomplete and unrelated to the progress in the thyroid state. The optic nerve involvement was responsible for visual failure in 3 patients (group B). Papilloedema, optic atrophy, constricted visual fields and ophthalmoplegias of various types were the main features and required early (and at times urgent) orbital decompression, muscle resections, myectomies, oral diuretics and oral and local corticosteroids. There were 4 patients in group C. In this group, the manifestations of corneal dystrophy and involvement of the macular area, optic disc and extra-ocular muscles were present in different combinations. Surgery with judicious use of corticosteroids and diuretics improved the vision to a certain extent. The improvement in this group was slower and incomplete compared to that in the other 2 groups.

Pathogenesis

The pathogenesis of ocular changes is still an enigma. The biopsy and post-mortem specimens of orbital tissue of human and experimental animals have shown an increase in the ground substance of the connective tissue, hyaluronic acid, mast cells, fibroblasts and lymphocytes. The histopathological

picture is consistent with pathological non-inflammatory immune infiltration. Thyroid stimulating immunoglobulins (TSI) appear to be responsible. Thyrotrophic hormone (TSH), exophthalmos-producing substance (EPS), and long-acting thyroid stimulator (LATS) have also been incriminated in the aetiopathogenesis of ocular manifestations (Adams and Purves, 1957; Dobyns, Wright and Wilson, 1961; Kriss *et al.*, 1967; McKenzie and McCullagh, 1968). Two recent studies have strengthened the impression that eye disorders are systemically related (Winand, 1968; Pisarev, Altschuler and Davison (1968). Depending upon the degree of exophthalmos and lagophthalmos, other complications such as exposure keratitis, corneal ulceration, severe hypopyon keratitis, and even panophthalmitis may result. The heavy and congested lids pressing on the cornea also contribute to corneal ulceration. Ophthalmoplegia is a troublesome complication and responds poorly to treatment. The anatomical position of the extra-ocular muscles is such that with their sheaths and orbital fascia they form a cone which is anchored to the orbit posteriorly and the base is formed by the eye. When the intra-orbital pressure is increased experimentally, both exophthalmos and immobility of the eye result (Poppen, 1953). The levator palpebrae superioris muscle is not stretched by the rise of intra-orbital tension and is rarely paralysed. This is attributed to the fact that its anterior insertion in the upper lid is mobile, not fixed. As the process advances, the affected muscles become fibrotic and short, leading to a fixed strabismus. The inferior rectus is the muscle which is most commonly involved. Bilateral shortening of this muscle accounts for the limitation in the upward movement commonly seen in clinical practice. With extensive muscle involvement the globe may be virtually immobile and the eyes are usually fixed in a downward squint. Very rarely the eye may be fixed in other positions. With increased intra-ocular pressure and overfilling of the orbit, the eyes become congested and the conjunctiva is glossy and waterlogged. Later it is thrown into folds along the free border of the lower lid. Subconjunctival haemorrhage and even glaucoma may result. The vision may fail from errors of refraction, corneal complications or optic nerve involvements. The optic nerve may be affected in the absence of severe proptosis. Increased intra-ocular pressure with resultant elevated pressure at the apex of the cone interferes with the blood supply of the optic nerve resulting in optic atrophy and irreversible visual loss. Poppen (1953) observed that increased tissue bulk confined in the region of the annulus of Zinn, where there was not enough fat to allow self-decompression by fat absorption, resulted in

pressure on the optic nerve, compromising its blood supply. Thus, in a patient who already has vascular disease, the vascular change could easily be precipitated. The visual prognosis in older patients and in those with arterial disease such as atherosclerosis and diabetes mellitus is, therefore, poor (Day and Carroll, 1962).

Treatment

Therapy is empirical and the main aim is to prevent corneal ulceration and optic nerve involvement. Simple lubrication drops such as 0.5% methyl cellulose, and ophthalmic ointments may be used to help prevent drying. Eye pads with paraffin gauze dressings over the closed eyelids may be applied at night if there is incomplete closure of the eyelids. Antibiotics may be used locally for infection. Guanethidine drops (Crombie and Lawson, 1967) of 5% solution may be used to relieve eyelid retraction. Subconjunctival or retrobulbar injections of methylprednisolone had not given very encouraging results (Garber, 1966). Systemic steroid therapy has proved useful and sometimes in serious cases where the optic nerve is involved or corneal complications threaten, high doses of steroids given for a short period (prednisone 120 to 140 mg daily for 7 days and gradually tapered off) may bring about the desired results (Werner, 1966). Glucocorticosteroids depress mucopolysaccharide synthesis and have a suppressive effect on the immune cells. Diuretics mobilize and promote the excretion of salt and water retained by the hydrophilic mucopolysaccharides and are useful. The role of immunosuppressive therapy is doubtful (Werner and Platman, 1965). Orbital decompression is undertaken when steroids are ineffective or contraindicated owing to systemic or local conditions. It is also advised when there is marked papilloedema, macular oedema or pressure on ciliary arteries manifesting as diminished visual acuity, field loss and marked increase in intra-ocular pressure. Classically, orbital decompression involves the removal of either the lateral wall or the roof of the orbit. More recently a transantral approach has been reported as giving good results (Ogura, Wessler and Avioli, 1971). By this method, the lateral wall of the ethmoidal sinuses and the roof of the maxillary sinus are removed. Surgical interference is not likely to benefit ocular movements as the muscle involvement is due to local infiltration of the muscle itself. An appropriate muscle resection and myectomy may help in a non-progressive phase. Radiotherapy to the pituitary, or hypophysectomy are no longer recommended. External irradiation of the orbital tissue is considered useful although its evaluation needs confirmation. Donaldson and Bagshaw (1972) have reported rapid and beneficial

effects by highly collimated supravoltage radiation of the retro-orbital space. Ravin, Sisson and Knapp (1975) advise that orbital radiotherapy should be considered as an initial therapeutic approach to the optic neuropathy of Graves' disease. Treatment of a hypermetabolic state should be properly monitored and gradual progress in a hyperthyroid condition should be ensured to avoid hypothyroidism. In fact, the patient may even be allowed to be mildly hyperthyroid until eye complications terminate spontaneously or with treatment.

Conclusion

Corneal oedema and infiltration, ophthalmoplegia and optic nerve involvement are the usual factors responsible for the heterogeneity of visual failure in Graves' disease. Usually more than one factor is responsible. The integrity of the cornea must be maintained with local antibiotics, large central tarsorrhaphy, orbital decompression (lateral or transfrontal), and steroids. With treatment, corneal infiltration may improve, visual acuity increase but proptosis, lid retraction and ophthalmoplegia usually persist. When the treatment is delayed, visual failure may lead to total blindness. A close and co-ordinated team approach by an endocrinologist and ophthalmologist is desirable for an effective treatment of ophthalmopathy.

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