CLINICAL RESEARCH

A specific IgG in Graves' ophthalmopathy and its relation to retro-orbital and thyroid autoimmunity

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Abstract

An IgG (ophthalmopathic immunoglobulin) that binds to retro-orbital antigen was identified in serum from patients with active Graves' ophthalmopathy, and its nature and specificity were investigated. Dose related binding of this immunoglobulin to retro-orbital antigens prepared from guinea pig harderian gland or porcine eye muscle was found, which could be abolished by prior incubation with antigen. The immunoglobulin did not bind to thyroid membranes, thyroid microsomes, or thyroglobulin or interact with liver, skeletal muscle, or fat membranes. Serum with high activity of thyrotrophin binding inhibiting immunoglobulin did not react with retro-orbital antigen, and this activity was not affected by preincubation of the serum with retro-orbital antigen. Thyroid stimulating hormone was also without effect on retro-orbital antigen.

It is concluded that Graves' ophthalmopathy is associated with a specific ophthalmopathic immunoglobulin that reacts with retro-orbital antigen as distinct from thyroid antigens, and that the autoimmune response is directed towards retro-orbital antigens. This suggests that the ophthalmopathy is an entity distinct from autoimmune thyroid disease.

Introduction

The association of ophthalmopathy with Graves' disease is well known, but, whereas the pathogenesis of hyperthyroidism has

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become clear in recent years, the explanation for the ophthalmopathy has been elusive. Graves' ophthalmopathy occurs in patients with hyperthyroidism (active or treated), occasionally with primary hypothyroidism, and sometimes in the absence of thyroid disease. Therefore it has been postulated that it is a distinct organ specific autoimmune disease. Current treatment is not very satisfactory, and improved management will depend on a better understanding of the pathogenesis. To this end there have been several studies of retro-orbital antigens and of T cell or humoral responses to them: cell mediated immunity has been found in patients with ophthalmic Graves' disease using guinea pig or human retro-orbital antigens[1][2]; monoclonal antibodies were used to study various human retro-orbital antigens[3]; and circulating autoantibodies were found using a soluble human eye muscle antigen.

In this study we investigated the relation of ophthalmopathy to thyroid disease by examining, firstly, the specificity of the binding of ophthalmopathic immunoglobulin to retro-orbital antigens and, secondly, the interactions of thyroid antibodies, including the receptor antibody responsible for hyperthyroidism, with retro-orbital antigens.

Methods

SERUM SAMPLES

For this study laboratory standards of ophthalmopathic immunoglobulin were used. They were obtained from two patients with severe ophthalmopathy and were selected from several serum samples known to contain easily detectable ophthalmopathic immunoglobulin because they were free of microsomal and thyroglobulin antibodies.

Case 1—Serum containing ophthalmopathic immunoglobulin activity was obtained from a woman born in 1923 who developed hyperthyroidism and exophthalmos in 1950. She underwent thyroidectomy but thereafter required antithyroid drugs, and subsequently she received external irradiation to the neck followed by three doses of iodine-131. Hyperthyroidism persisted, and in 1975 she received a further 16 mCi dose of [131]I. The ophthalmopathy deteriorated, and she was treated with external irradiation to the orbits in 1975; steroids were started in 1976, and she underwent corneal grafting and eventual unilateral enucleation in 1978. In 1983 she was euthyroid while taking thyroxine 50 μg daily. Her remaining eye showed continuing active ophthalmopathy. There was a strong family history of auto-

immune thyroid disease: two of her five siblings, her mother, and three of her mother's eight siblings were affected. She carried the HLA A1, B8, DR3 haplotype.

Case 2—Serum containing ophthalmopathic immunoglobulin activity was obtained from a man born in 1912 who was healthy until March 1981, when, after undergoing nephrectomy for hydronephrosis, he complained of sore, prickly eyes. By July 1981 he had pronounced bilateral proptosis and active ophthalmopathy but was clinically and biochemically euthyroid. In August the ophthalmopathy was more severe with ophthalmoplegia and he had become minimally thyrotoxic (serum thyroxine concentration 149 nmol/l (11·6 μg/100 ml) (normal range <150 nmol/l (<11·7 μg/100 ml)), triiodothyronine concentration 4·7 nmol/l (3·1 ng/ml) (normal range <3 nmol/l (<2·0 ng/ml)), and flat response to a thyrotrophin releasing hormone test); an isotope scan showed as light diffuse increase in thyroidal uptake.

Serum was also obtained from patients with a high titre of thyrotrophin binding inhibiting immunoglobulin but without ophthalmopathy, as well as from healthy subjects. All serum samples were stored in aliquots at −40°C. Thyroglobulin and microsomal antibodies were assayed with Fujizoki kits. Thyrotrophin binding inhibiting immunoglobulin was measured in a receptor binding assay,[4] modified by the use of solubilised receptors for thyroid stimulating hormone.

PREPARATION OF ANTIGEN

Retro-orbital fractions were prepared from porcine retro-orbital muscle and guinea pig harderian glands and used as antigens to coat microwell plates for an enzyme linked immunosorbent assay. Porcine retro-orbital muscle was used in preference to human tissue as adequate amounts of fresh tissue are readily available. Guinea pig harderian gland was also examined as it has been used as a model in several previous studies of Graves' ophthalmopathy.[5-7]

Retro-orbital tissue was dissected free of fat and connective tissue and homogenised in five volumes of buffer containing trometamol (TRIS) 10 mmol/l and sodium chloride 50 mmol/l (pH 7·4) in a polytron blender at 4°C. The homogenates were centrifuged at 800 *g* for 10 minutes at 4°C and the resulting supernatant centrifuged at 10 000 *g* for 20 minutes at 4°C. The pellet from this centrifugation was resuspended in trometamol-sodium chloride buffer and used in experiments of membrane absorption. The supernatant from the 10 000 *g* spin was further centrifuged at 100 000 *g* for 60 minutes at 4°C and the pellet resuspended in trometamol-sodium chloride buffer and used to coat microwell plates. The protein concentrations of the membrane fraction and the 100 000 *g* retro-orbital antigen were estimated by the method of Lowry. Both fractions were stored in aliquots at −70°C until use.

For specificity studies tissue was obtained from guinea pig and porcine thyroid, liver, heart muscle, skeletal muscle, and fat. After homogenisation 10 000 *g* and 10 000 *g* fractions were prepared as above and used either to coat microwell plates for an enzyme linked immunosorbent assay or for experiments of immunoglobulin absorption. Human thyroid microsomes were prepared as previously described,[8] and porcine thyroglobulin was obtained commercially (Sigma).

Pretreatment of serum by absorption to porcine red blood cells was as follows. Pig blood was semidiluted in Alsever's solution (0·42% sodium chloride, 0·8% sodium citrate, 2·05% glucose) and centrifuged at 800 *g* for five minutes at 4°C; the pellet was washed three times in 0·95% saline and finally resuspended in saline. The suspension was incubated with serum for 60 minutes at 37°C, the red blood cells then pelleted, and the supernatant used in the enzyme linked immunosorbent assay.
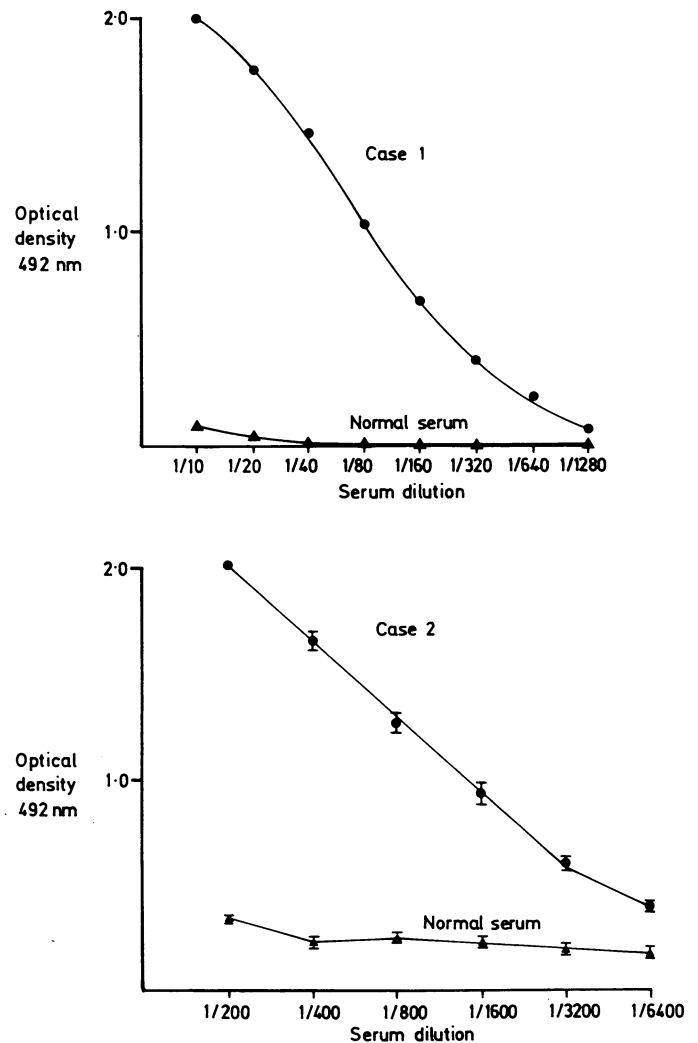
ENZYME LINKED IMMUNOSORBENT ASSAY

Microwell plates (Flow, Limbro) were coated with retro-orbital antigens (10 μg/l) in carbonate buffer pH 9·6 by overnight incubation at 4°C. Serum was applied diluted in phosphate buffer pH 7·4 (120 minutes' incubation at room temperature). The enzyme used was horseradish peroxidase conjugated to porcine antihuman IgG (Orion Diagnostics) (120 minutes' incubation at room temperature), with *o*-phenylene diamine as substrate (30 minutes' incubation at room temperature in the dark). Optical densities (492 nm) were measured (Flow Titertek Multiskan) on triplicates for each sample with appropriate controls.

Results

Neither of the standard sera showing ophthalmopathic immunoglobulin activity contained detectable thyroglobulin antibodies or microsomal antibodies at any stage of serial sampling. Both sera had demonstrable activity of thyrotrophin binding inhibiting immunoglobulin (55 units in case 1, 31 units in case 2 (normal reference range <15 units)).

The figure shows the dose dependent relation between the concentration of ophthalmopathic immunoglobulin (case 1) and binding

Top: Binding of ophthalmopathic immunoglobulin (case 1) or IgG in pooled normal serum to guinea pig harderian gland antigen (100 000 *g* fraction; 10 μg/ml), measured by optical density of microwells in enzyme linked immunosorbent assay. Bottom: Binding of ophthalmopathic immunoglobulin (case 2) to porcine eye muscle antigen (100 000 *g* fraction; 10 μg/ml).

to guinea pig harderian antigen and the similar relation between ophthalmopathic immunoglobulin (case 2) and porcine retro-orbital antigen. Specific binding was detected at serum dilutions of up to 1/1280 and 1/6400 respectively. The absence of specific binding of IgG from pooled normal serum is also shown for both antigens.

Individual serum samples from 40 healthy subjects (diluted 1/100) gave a normal range of optical densities of <0·29 nm with guinea pig harderian antigen and of <0·37 nm with porcine retro-orbital muscle antigen.

Table I shows binding of serum from case 1 and of pooled normal serum to 100 000 *g* antigen preparations from various guinea pig tissues coated on microwell plates. Only in the case of the retro-orbital antigen prepared from harderian glands was binding of serum containing ophthalmopathic immunoglobulin activity appreciably

TABLE I—*Mean (SD) binding of serum containing ophthalmopathic immuno-globulin (OIg) and of pooled normal serum (n=3) to various guinea pig tissue 100 000 g fractions coated on to microwell plates at concentrations of 5, 10, and 20 µg/ml (optical density at 492 nm)*

Coating antigen	Concentration (µg/ml)	Pooled normal serum	Serum containing OIg (case 1)
None		0·159 (0·030)	0·063 (0·011)
Harderian gland	5	0·408 (0·004)	1·073 (0·022)
	10	0·472 (0·003)	1·892 (0·049)
	20	0·466 (0·009)	>2
Thyroid	5	0·538 (0·009)	0·124 (0·016)
	10	0·557 (0·021)	0·138 (0·017)
	20	0·625 (0·020)	0·186 (0·025)
Liver	5	0·404 (0·006)	0·327 (0·011)
	10	0·453 (0·022)	0·442 (0·031)
	20	0·446 (0·026)	0·639 (0·025)
Skeletal muscle	5	0·548 (0·016)	0·440 (0·010)
	10	0·608 (0·032)	0·408 (0·040)
	20	0·726 (0·035)	0·399 (0·0)
Heart	5	0·425 (0·014)	0·532 (0·027)
	10	0·429 (0·009)	0·267 (0·017)
	20	0·472 (0·012)	0·334 (0·022)
Fat	5	0·489 (0·025)	0·322 (0·010)
	10	0·580 (0·012)	0·487 (0·009)
	20	0·550 (0·022)	0·651 (0·024)

greater than that of pooled normal serum, indicating specificity for retro-orbital tissue. The greater degree of binding of pooled normal serum to thyroid 100 000 g antigen compared with ophthalmopathic immunoglobulin is unexplained but might reflect undetected thyroid antibodies in a member of the normal pool. The binding of serum from case 2 to porcine thyroid, liver, heart muscle, skeletal muscle, and fat was also investigated, and in all tissues examined was slightly greater than the binding of pooled normal serum; but the binding of serum from case 2 to retro-orbital antigen was two to three times greater than binding to other tissue antigens. The serum was pretreated by absorption to porcine red blood cells to reduce non-specific binding to porcine tissues (Forssman antibody effect), but this had no effect on binding to porcine retro-orbital antigen.

The tissue specificity of ophthalmopathic immunoglobulin was further investigated by attempting to absorb out antigen binding activity by preincubation of serum with membrane preparations from various tissues. Preincubation of serum from case 1 (0·045 µl/ml) with increasing concentrations of harderian gland membranes considerably reduced IgG binding to 100 000 g harderian antigen. Preincubation with guinea pig tissue membranes prepared from thyroid, liver, skeletal muscle, and fat had no appreciable effect on IgG binding, with the exception of liver membranes at high concentration (10 mg/ml). Similarly, prior incubation with human thyroid membranes at concentrations of up to 6 mg/ml had no effect on activity of ophthalmopathic immunoglobulin. Porcine thyroglobulin and human thyroid microsomes also failed to neutralise activity of ophthalmopathic immunoglobulin. The binding of serum from case 2 to porcine retro-orbital antigen was considerably reduced by preincubation with membranes prepared from porcine eye muscle but not by membranes prepared from porcine thyroid, liver, heart muscle, skeletal muscle, or fat or by human thyroid membranes, human thyroid microsomes, or porcine thyroglobulin.

Preincubation of serum containing ophthalmopathic immunoglobulin with retro-orbital membranes had no effect on activity of thyrotrophin binding inhibiting immunoglobulin (table II). The serum was preincubated with guinea pig harderian gland, thyroid, and skeletal muscle membranes (1 mg/ml); after centrifugation IgG was prepared from the supernatant and thyrotrophin binding inhibiting immunoglobulin estimated. Preincubation with harderian gland and skeletal muscle membranes had no effect on activity of

TABLE II—*Mean (SD) thyrotrophin binding inhibiting immunoglobulin activity of serum containing ophthalmopathic immunoglobulin (OIg) (expressed as % inhibition of binding of thyroid stimulating hormone labelled with [125]I (^{125}I-TSH) after incubation with harderian gland, thyroid, and skeletal muscle membranes (10 000 g fractions, 1 mg/ml)*

	% inhibition of ^{125}I-TSH binding
Pooled normal serum	0·5 (2·1)
Serum containing OIg	55·0 (3·0)
Serum containing OIg after incubation with membrane preparations from:	
Thyroid	36·5 (2·5)*
Harderian gland	55·0 (3·1)
Skeletal muscle	51·0 (3·8)

*Significance of difference from serum containing OIg: p<0·02.

thyrotrophin binding inhibiting immunoglobulin, whereas incubation with thyroid membranes reduced it (as measured by a reduced ability to inhibit binding of thyroid stimulating hormone labelled with ^{125}I to the hormone receptor). Furthermore, thyrotrophin binding inhibiting immunoglobulin obtained from eight patients with hyperthyroidism but without ophthalmopathy did not show any activity of ophthalmopathic immunoglobulin.

There was no binding of thyroid stimulating hormone to retro-orbital tissue. When plates coated with harderian antigen were preincubated with bovine thyroid stimulating hormone (Thytropar, Armour Pharmaceuticals) at concentrations of 0, 1, 10, and 100 U/l no appreciable change in binding of ophthalmopathic immuno-globulin to harderian antigen resulted (table III). Furthermore, the

TABLE III—*Effect of thyroid stimulating hormone (TSH) on binding of ophthalmopathic immunoglobulin to harderian antigen. Results expressed as means (SEM) (n at 3; optical density at 492 nm)*

	Preincubation concentration of TSH (U/l)*			
	0	1	10	100
Pooled normal serum	0·324 (0·03)	0·306 (0·014)	0·314 (0·016)	0·318 (0·028)
Serum containing ophthalmopathic immunoglobulin (case 1)	1·627 (0·014)	1·534 (0·022)	1·554 (0·016)	1·561 (0·036)

*Plates coated with harderian antigen (10 µg/ml) were preincubated (for 60 minutes at room temperature) with bovine TSH at different concentrations. Serum was diluted 1/100.

coincubation of thyroid stimulating hormone with ophthalmopathic immunoglobulin (2 mU bovine thyroid stimulating hormone/100 µl serum) in other experiments had no effect on binding of the immunoglobulin to retro-orbital antigens.

Discussion

In this study an IgG (ophthalmopathic immunoglobulin) associated with Graves' ophthalmopathy was shown to bind to retro-orbital antigens in a dose related manner; this effect was not observed with normal serum. The immunoglobulin could be removed by prior incubation with retro-orbital antigen. The retro-orbital antigen is distinct from thyroid antigen as little or no IgG binding to various thyroid antigens occurred and the immunoglobulin was not absorbed by prior incubation with different thyroid fractions; in particular, it was not related to microsomal antibody or thyroglobulin antibody. Ophthalmopathic IgG is also distinct from thyrotrophin binding inhibiting immunoglobulin and thyroid stimulating antibody, the antibody responsible for hyperthyroidism.[9] Prior incubation with thyroid particulate membranes had no effect on activity of ophthalmopathic immunoglobulin, and incubation of thyrotrophin binding inhibiting immunoglobulin with retro-orbital antigen did not reduce activity of the thyrotrophin binding inhibiting immunoglobulin. Samples with a very high titre of thyrotrophin binding inhibiting immunoglobulin from patients without exophthalmos did not have ophthalmopathic immunoglobulin.

In a series of patients with thyroid or eye disease, or both, ophthalmopathic immunoglobulin correlated with the presence of active ophthalmopathy (S Atkinson et al, paper submitted for publication). Earlier work suggested a possible role for thyroid stimulating hormone or thyroid stimulating hormone fragments in the pathogenesis of Graves' ophthalmopathy[10 11]; in our study, however, the hormone had no effect: it did not bind to retro-orbital antigen, its addition to samples containing ophthalmopathic immunoglobulin did not alter the response, and preincubation of retro-orbital antigen with thyroid stimulating hormone did not have any effect on the subsequent binding of ophthalmopathic immunoglobulin to antigen. Immunoglobulins specific to Graves' disease interact similarly with porcine thyroid tissue and with human thyroid,[12 13] suggesting antigenic similarity; thus the use of porcine retro-orbital eye muscle seemed reasonable.

Graves' ophthalmopathy is generally regarded as an organ specific autoimmune disease,[14] probably distinct from thyroid autoimmune disease though closely related to it. The pathogenesis is not known. It occurs most commonly with hyperthyroidism but is also found in patients with primary myxoedema, with Hashimoto's thyroiditis, or with no thyroid disease at all, and the severity of the condition does not correlate with thryroid function.[15-17] There is poor correlation of thyroid antibodies with ophthalmopathy, and in particular immunoglobulins specific to Graves' disease such as thyrotrophin binding inhibiting immunoglobulin and long acting thyroid stimulator protector are not found with any consistency.[16-18] Attempts to neutralise long acting thyroid stimulator with retro-orbital antigens were unsuccessful.[19] Our work supports the view that thyrotrophin binding inhibiting immunoglobulin, long acting thyroid stimulator, and long acting thyroid stimulator protector are not directly associated with Graves' ophthalmopathy and is consistent with the hypothesis that ophthalmopathy is a distinct entity.

There have been several previous attempts to show immune disturbance related to retro-orbital antigens. Munro et al showed cellular immunity, using the migration inhibition factor test, against retro-orbital antigens in patients with ophthalmopathy and found that this could be distinguished from the response of migration inhibition factor to thyroidal antigens in patients with autoimmune thyroid disease.[2] Our finding of a specific IgG, indicating a B cell response to retro-orbital antigens, is consistent with this. Konishi et al reported an affinity of retro-orbital muscle for thyroglobulin and for thyroglobulin-antithyroglobulin complexes[20]; Mullin et al found that the autoantigen in the migration inhibition factor test was chemically similar to thyroglobulin.[21] The importance of these findings is not clear, particularly as many patients have either no thyroglobulin antibody or no thyroid disease. In our study the IgG could not be absorbed with thyroglobulin even at high concentration. More recently, Kodama et al produced monoclonal antibodies to various retro-orbital antigens and used them to study the nature of the antigen in patients with ophthalmopathy.[3] They found a tendency for these monoclonal antibodies to eye muscle to cross react with skeletal muscle, and in one case there was cross reactivity with thyroid microsomes. Some patients with ophthalmopathy were observed to have circulating antibody (ophthalmopathic immunoglobulin) to soluble antigen derived from eye muscle.

Our work confirms the finding of an ophthalmopathic immunoglobulin in serum of patients with Graves' ophthalmopathy and shows the specific nature of this immunoglobulin as distinct from thyroid antibodies, suggesting that the autoimmune response is directed towards specific retro-orbital antigen. As yet there is no evidence that ophthalmopathic immunoglobulin is itself pathogenic, but the ability to detect this immunoglobulin will facilitate further studies of the pathogenic mechanisms for the development of ophthalmopathy, which should ultimately lead to more rational and more effective approaches to its management.

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ONE HUNDRED YEARS AGO   It is by no means an uncommon thing now for a schoolmaster to be summoned before magistrates on a charge of assaulting a pupil. There seems to be a misapprehension in the minds of many people as to what are the rights of schoolmasters and their pupils respectively in this matter. At common law, a master is considered as standing in loco parentis to his pupil, and is entitled to chastise him in the same way as a father might. This position may be varied by agreement between the parties; as, if a father stipulates with the schoolmaster that his son is not to be subject to corporal punishment, or if the rules of the school forbid the master administering it, or only allow him to do so in certain specified instances. In the absence of any such agreement, however, a master may, in his own discretion, administer reasonable chastisement to his pupils. If a complaint be brought against him in a court of justice, the question which the court ought to consider is, how far the chastisement which was administered was or was not reasonable, having regard to the circumstances of each particular case. This question is often by no means easy to decide; and the decisions given by different courts are by no means easy to reconcile with one another. But a good deal of ill feeling might be spared, and cases might with advantage be kept out of court which now are brought there, if boys and their parents would remember that masters have, prima facie, a right to chastise their pupils, and that a charge of assault can only be maintained if the punishment be excessive. (British Medical Journal 1884;i:232.)