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Sympathetic Overactivity in the Development of Eyelid Retraction in a Patient with Euthyroid Graves' Disease Evaluated by Accommodation

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Abstract. It is known that measurement of accommodation is useful to evaluate the sympathetic activity of intraocular muscles. To find if sympathetic overactivity is involved in eyelid retraction in euthyroid Graves' disease, we measured accommodation in two patients with this disease, whose serum concentrations of free T3, free T4 and TSH were within reference ranges. Accommodation was measured with a computer-assisted infrared optometer with an iriscoder, and the results were expressed as the change in the eye's refractive power (in diopters) in response to the movement of a target beam. In patient 1, the accommodation amplitude was low, indicating sympathetic overactivity. This amplitude rose to near the reference range when timolol maleate drops were used, and the eyelid retraction disappeared when guanethidine drops were given. During the use of guanethidine drops, accommodation remained normal. In patient 2, who had normal accommodation, eyelid retraction did not change with guanethidine administration, but improved with intravenous methylprednisolone pulse therapy. These two cases suggested that even in euthyroid Graves' disease, eyelid retraction is caused by sympathetic overactivity, and pulse therapy with methylprednisolone may be effective for eyelid retraction when guanethidine drops are not effective.

Key words: Eyelid retraction, Euthyroid Graves' disease, Accommodation, Sympathetic overactivity, Guanethidine

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THE main cause of eyelid retraction in Graves' disease seems to be Müller's muscle overaction arising from sympathetic overactivity secondary to thyrotoxicosis [1]. However, such retraction is observed in euthyroid Graves' disease as well, perhaps because of severe proptosis or enlargement, fibrosis and scarring of the eyelid levator muscles [2, 3]. Sympathetic overactivity seems not to occur if hyperthyroidism is absent.

There have been few reports about autonomic nervous function of eyes in patients with Graves' disease [4, 5] but we reported recently that measurement of accommodation is useful to evaluate the sympathetic activity of intraocular muscles [6]. By this method, we found that accommodation in patients with hyperthyroid Graves' disease was lower than that of controls, indicating sympathetic overactivity in eyes of patients. To find whether sympathetic overactivity is involved in eyelid retraction in euthyroid Graves' disease, we measured accommodation in patients with this disease and examined the results in relation to response to treatment.

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Patients and Methods

Patients

Of the 328 patients with Graves' disease who visited Sumire Hospital at any time from January 1991 to May 1996, three patients were found to have euthyroid Graves' disease. Their serum free T3, free T4 and TSH concentrations were within reference ranges. Of those three patients, the two patients aged less than 40 years were selected for this study, because accommodation cannot be tested in patients aged 40 years or more [7].

Measurement of accommodation

Accommodation was measured with a computer assisted infrared optometer with an iriscoder (Nidek, Aichi, Japan) as described elsewhere [6]. In brief, accommodation was measured in the slow mode with the target beam moving 10 diopters away from the original point at a speed of 0.2 diopter/sec. The results were expressed as the change in the refractive power of the eye (in diopters) in response to the movement of the light beam.

Exophthalmos was measured with a Hertel exophthalmometer.

Measurement of thyroid function

The serum levels of free T3 and free T4 were assayed with Amalex-mab free T3, T4 kit (Ortho-Clinical Diagnostics, Tokyo, Japan), and that of TSH was measured with a highly sensitive immunoradiometric assay kit (TSH RIA kit; Dainabot Co. Ltd. Chiba). The minimum detectable value of serum TSH is 0.02 mU/L. Thyrotropin-binding-inhibiting immunoglobulin (TBII) was measured by a radioreceptor assay (TRAb kit, RSR Ltd., Cardiff, UK). Thyroid stimulating antibody (TSAb) was measured in terms of the amount of cAMP produced by cultured cells of porcine thyroid by the method described by Kasagi *et al.* [8]. Titers for microsomal autoantibody particle agglutination (MCPA) and thyroglobulin autoantibody particle agglutination (TGPA) were assayed with commercial kits (Serodia AMC and ATG, Fuji Revio, Tokyo). Thyroglobulin autoantibody (TgAb) and thyroid peroxidase autoantibody (TPOAb) were measured by immunoprecipitation methods with labeled Tg and TPO (TgAb and TPOAb "Cosmic", Cosmic Corp., Tokyo).

The reference ranges (mean−2SD to mean+2SD) used for free T3, free T4, and TSH were 2.37 to 8.05 pmol/L, 7.3 to 28.1 pmol/L, and 0.34 to 3.50 mU/L, respectively, and those for TBII, TSAb, MCPA, TGPA, TgAb and TPOAb were less than 15.0%, less than 180%, less than 100, less than 100, less than 0.3 U/ml and less than 0.2 U/ml, respectively.

Results

Clinical results of the two subjects are summarized in Table 1. Free T3, free T4 and TSH levels were within the reference ranges and there was no history of hyperthyroidism in either patient. In patient 1, serum TSH concentrations before and 30 min after intravenous administration of 500 μg of synthetic thyrotropin releasing hormone were 1.93 mU/L and 20.21 mU/L, respectively. A small goiter could be palpated in both patients, but TBII, MCPA, and TGPA were below their cut-off levels. The diagnosis of Graves' ophthalmopathy was based on the TSAb level in patient 2. In patient 1, both TBII and TSAb were negative at the first examination, but the TSAb became positive (191%) 3 years later. The TPOAb was positive and the biopsy findings by fine needle

Table 1. Clinical findings from the two women with euthyroid Graves' disease

	Patient 1	Patient 2
Age (years)	37	19
Goiter (degree)	2	1
Free T_3 (pmol/L)	6.05	4.63
Free T_4 (pmol/L)	16.3	18.1
TSH (mU/L)	2.04	0.42
TBII (%)	2.6	9.3
TSAb (%)	62*	245
TGPA (dilution factor)	<100	<100
MCPA (dilution factor)	<100	<100
TgAb (U/ml)	<0.3	<0.3
TPOAb (U/ml)	0.7	3.6
FNAB**	Lymphocytic thyroiditis	Not done

* TSAb became positive (191%) 3 years later.
** Fine needle aspiration biopsy

aspiration being compatible with lymphocytic thyroiditis in patient 1. Therefore, the diagnosis of Graves' ophthalmopathy in patient 1 was made by these findings in addition to exophthalmos and typical eyelid retraction.

Both patients visited our hospital complaining of eye problems. Patient 1 reported retraction of the left upper eyelid of 6 months duration and patient 2 reported exophthalmos and retraction of the right upper eyelid of 2 months duration (Fig. 1a). Measurements by exophthalmometry were 18.0 and 19.0 mm for the right and left eyes of patient 1, and 19.0 and 18.0 mm for patient 2. Computed tomography of the orbits showed no abnormalities in patient 1 and enlargement of the superior rectus muscle of the right eye in patient 2. Both patients did not have cornea involvements, optic nerve dysfunction, or abnormalities in movement of the eyeball. Clinical activity score judged according to the classification of American Thyroid Association [9] was 0 in patient 1 and 1 in patient 2.

Patient 1

The results of measurements of accommodation are shown in Fig. 2. In healthy subjects, the refractive power first increases and then decreases as target moves [6], but in this patient, the refractive power did not increase as target moved. The mean accommodation amplitude for 12 healthy subjects was 6.24 ± 0.83 diopters ($\pm$SD) [6], but the amplitude of right eye of this patient was 3.2 diopters and that of the left eye was 2.0 diopters, indicating sympathetic overactivity in both eyes (Fig. 2a). The accommodation rose to 4.0 diopters in the right eye and 4.5 diopters in the left eye when timolol maleate drops were used (Fig. 2b), and eyelid retraction disappeared with use of guanethidine drops for one week (Fig. 1b, left). When guanethidine drops were being used, accommodation was normal (Fig. 2c), but when the

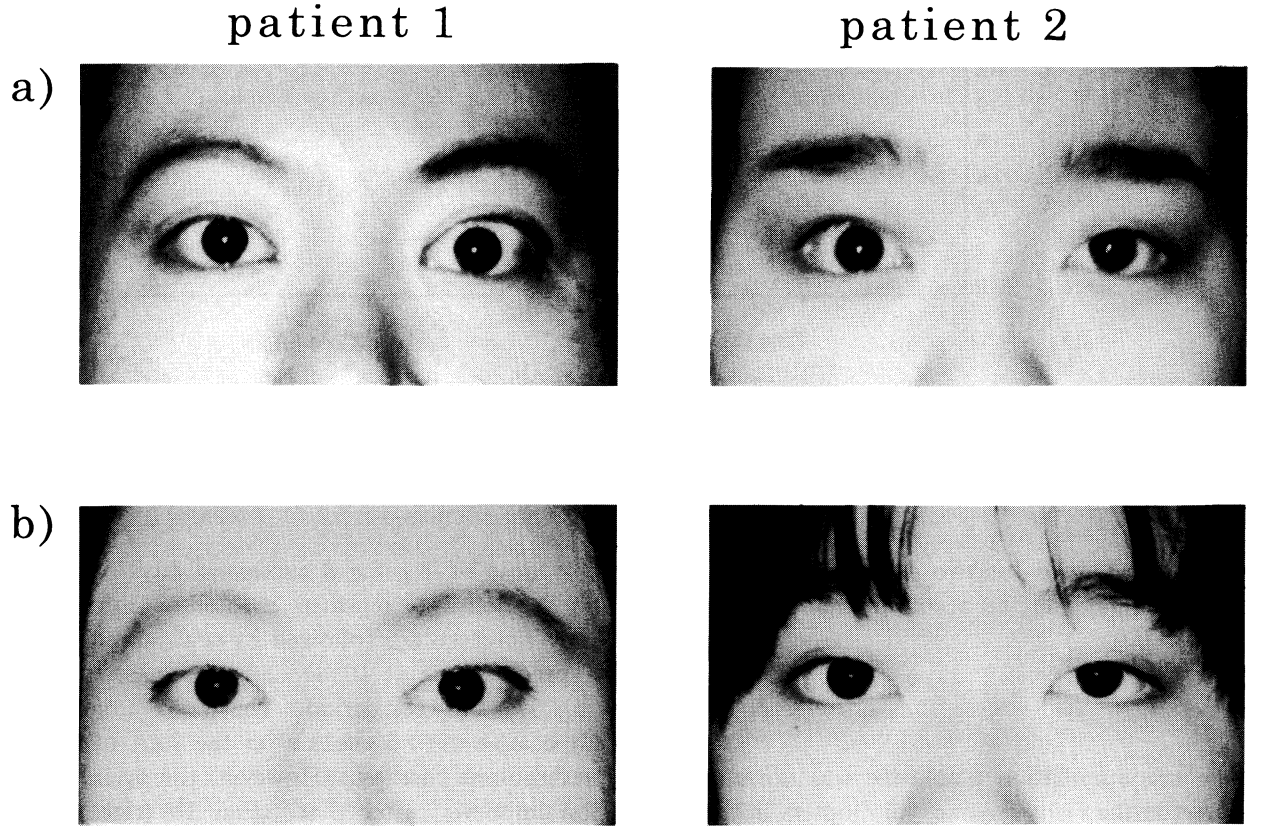

Fig. 1. Left; appearance of patient 1, a, before treatment, b, after one month of local guanethidine (5%) therapy with dosage of one drop a day. Right; appearance of patient 2, a, before treatment, b, two months after methylprednisolone therapy started.

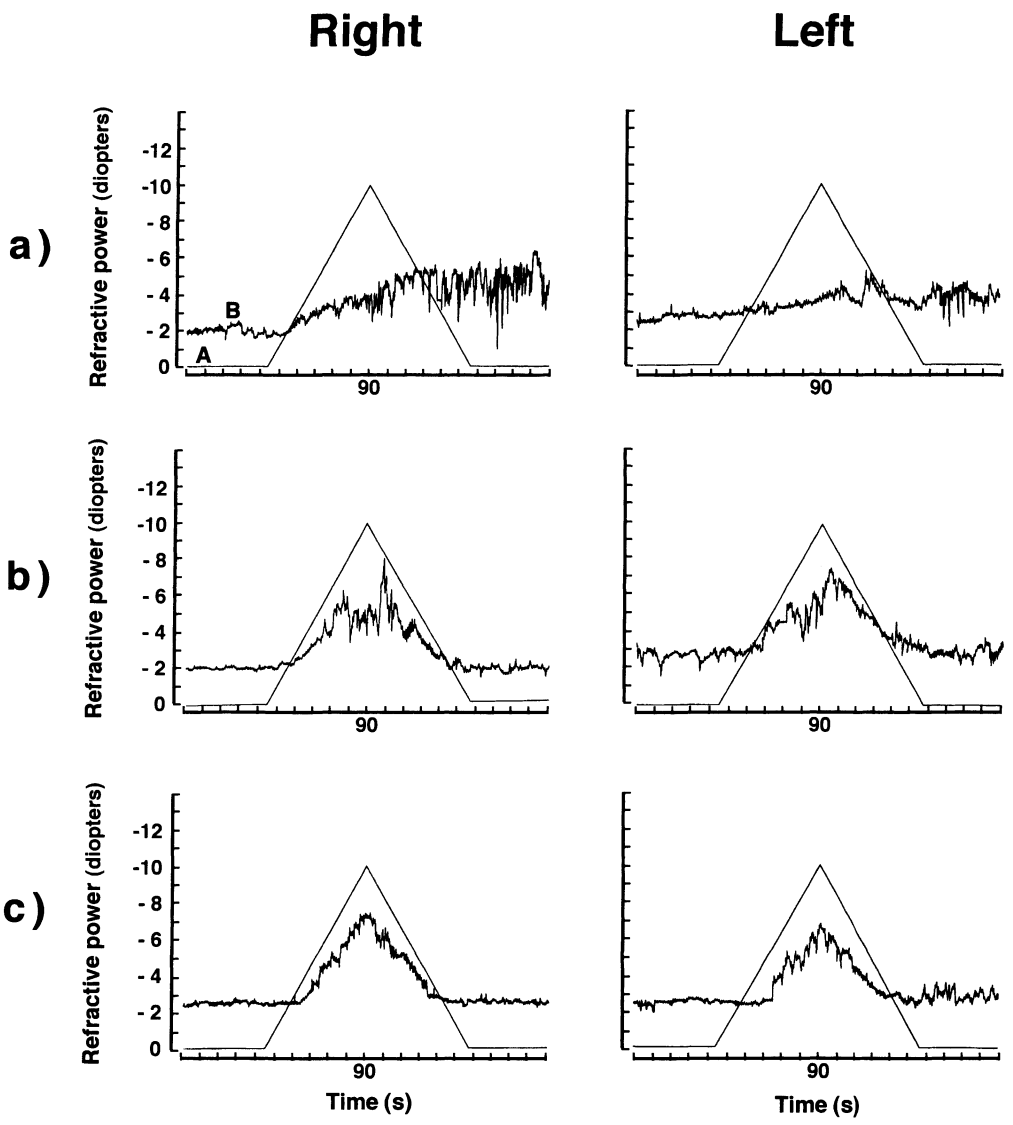

Fig. 2. The results of accommodation of patient 1. The results are expressed as the change in refractive power of the eye (in diopters) while the target beam is moving. A and B shows the movements of target and change in refractive power of the patient, respectively. a, before treatment, b, 30 min after treatment with drops of timolole maleatre, beta-adrenergic recepter antagonist, c, during the treatment with drops of guanethidine.

drops were stopped for two days, eyelid retraction appeared again and the accommodation amplitude decreased.

Patient 2

The accommodation amplitude was normal, 5.5 diopters in the right eye and 4.6 diopters in the left eye. The eyelid retraction did not change with use of guanethidine drops for two months. Methylprednisolone was therefore injected intravenously at the daily dose of 1 g for 3 successive days. This administration was repeated a total of 3 times with 4 days intervening, followed by oral administration of prednisolone at 10 mg daily, decreased to 5 mg daily over a 3-week period. The eyelid retraction did not change until 5 weeks after the start of methylprednisolone therapy. However, the eyelid retraction improved after that. Fig. 1b (right) shows patient 2, two months after methylprednisolone therapy started. Hyperthyroidism developed one year and two months after methylprednisolone ther-

apy started but eyelid retraction did not appear. Eyelid retraction has not recurred to date, four years after methylprednisolone treatment was terminated.

Discussion

We reported here the results of accommodation and the effects of treatment on eyelid retraction in two patients with euthyroid Graves' disease. It was demonstrated that one patient (patient 1) had low accommodation and her eyelid retraction disappeared when guanethidine drops were given, and another patient (patient 2) had normal accommodation and her eyelid retraction did not change with guanethidine drops but improved with methylprednisolone pulse therapy.

The increase in accommodation amplitude is caused by a contraction of ciliary muscles, which is mainly regulated by parasympathetic nerves. Therefore, the low accommodation amplitude in patient 1 suggested that either the parasympathetic nerve is being prevented from functioning or that some force is acting in opposition to its effect. However, there is no evidence to suggest that the parasympathetic nerve is being prevented from functioning. Although the parasympathetic nerve predominates, ciliary muscles also receive sympathetic innervations mediated by the action of noradrenaline on beta adrenoceptors, which is inhibitory. Therefore, the low accommodation of patient 1 seems to be caused by sympathetic overactivity because it returned to normal when a beta-adrenergic antagonist was used. In addition to this evidence, disappearing of eyelid retraction when guanethidine drops were given suggested that eyelid retraction of this patient was caused by sympathetic overactivity.

It is not clear why only one eyelid was retracted although sympathetic overactivity was observed in both eyes of this patient. There is no difference in accommodation amplitude between Graves' patients with and without eyelid retraction [6], so eyelid retraction seems not to be caused by sympathetic overactivity alone. Some additional factor, which may increase the sensitivity of Müller muscles to sympathetic stimuli, is necessary for eyelid retraction.

The most important finding reported here is the sympathetic overactivity of the eye in this patient who was completely euthyroid. She had no other signs of sympathetic overactivity such as tachycardia or increased sweating, and there was no history of hyperthyroidism. Therefore, the sympathetic overactivity of the eye seems not to be caused by abnormal thyroid function. The mechanism is not known, but an autoimmune reaction to Müller muscles might have increased the sensitivity of beta-receptors of these muscles to sympathetic stimuli, since the factors that cause the pathogenetic condition known as Graves' disease seem to be autoimmunity and hyperthyroxinemia. While this paper was being prepared, corticosteroid drops were tried in this patient. Eyelid retraction disappeared after two weeks of use of Rinderon A drops (Shionogi Pharmaceutical Co. Ltd.) containing betamethasone sodium phosphate and fradiomycin sulfate, twice daily, but retraction appeared again one month after the treatment was stopped.

In patient 2, the accommodation being normal and the eyelid retraction not improving when guanethidine drops were given, showed that eyelid retraction in this patient was not caused by sympathetic overactivity. However, her eyelid retraction disappeared with intravenous methylprednisolone therapy. Some change in the levator palpebrae superioris muscle seems to have been present, since the superior extraocular muscle was enlarged. The kind of change was not clear, but it was not only inflammation [10] because methylprednisolone took 5 weeks to take effect. The effect of steroid pulse therapy on eyelid retraction in euthyroid Graves' disease has not been reported [11, 12]. Intravenous methylprednisolone pulse therapy may thus be useful in treating eyelid retraction of euthyroid Graves' disease not related to sympathetic overactivity.

The results of this study also suggest that measurement of accommodation gives information useful for selection of treatment for eyelid retraction in euthyroid Graves' disease, as one problem in topical use of guanethidine eye drops is the unpredictable effect even in hyperthyroid Graves' disease [13].

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