NOTE

Treatment of Graves' Ophthalmopathy by Steroid Therapy, Orbital Radiation Therapy, Plasmapheresis and Thyroxine Replacement

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Abstract

Thirteen patients with moderately severe ophthalmopathy due to Graves' disease were treated by steroid therapy, supervoltage orbital radiotherapy, plasmapheresis and thyroxine replacement. All patients complained of chemosis, ocular pain and diplopia. The mean value of proptosis was 21.3 mm. Eleven patients (84.6%) showed some improvement, but the effect was mostly on the symptoms of orbital soft tissue involvement. The effect on proptosis was rather unsatisfactory. In six patients (46.2%) proptosis decreased by 2.3 mm on the average, but they still had more noticeable exophthalmos than patients with Graves' disease without infiltrative ophthalmopathy. For regression of proptosis, radiation therapy was the most beneficial therapeutic regimen in this study, especially in the patients who received the treatment shortly after the beginning of malignant exophthalmos.

Many therapeutic approaches to malignant exophthalmos have been reported, but none of them has gained sufficient acceptance to be regarded as a standard method of therapy. Systemic administration of steroids in large quantities (prednisolone 60-120 mg/day) often improves orbital inflammatory signs. Improvement of ophthalmoplegia, papilledema and optic neuritis have also been reported (Brown et al., 1963; Werner, 1966). Recently, highly collimated supervoltage radiation of the retro-orbital space has been applied, with seemingly rapid and beneficial effects, to infiltrative and inflammatory manifestations (Donaldson et al., 1973; Corvington et al., 1977). On the other hand, Teng et al., (1980) reported somewhat disappointing results in that only 25% of the patients had improved proptosis after orbital radiotherapy. Dandona et al. (1981) tried plasmapheresis for the treatment of exophthalmos and reported it to be effective. Danowski et al. (1971) suggested that prescription of adequate doses of thyroid hormone at the time of treatment of thyrotoxicosis is beneficial. The present study reports our results with steroid therapy, supervoltage orbital radiotherapy, plasmapheresis and thyroxine replacement therapy in 13 patients with moderately severe ophthalmopathy.

Materials and Methods

Thirteen patients (9 males and 4 females) were diagnosed as having malignant exophthalmos, according to the diagnostic criteria of Hormone Receptor Disease Research Committee, Japan (Torizuka et al., 1981). All patients complained of chemosis, ocular pain and diplopia. The mean value for proptosis was 21.3 mm (ranging from 18-23 mm). They had marked hypertrophy of the extracocular muscles on ultrasonograph. The mean value for the muscle
index was more than twice that of the controls (patients, 7.2±2.1, n=13: controls, 3.1±1.3, n=12, p<0.001). Of 13 patients, one received steroid therapy, 5 steroid therapy and subsequent radiation therapy, 2 plasmapheresis and successive radiation therapy, 2 radiation therapy alone, and 3 thyroxine replacement. Ten patients who received steroid therapy, orbital radiotherapy and/or plasmapheresis were given thyroxine (100 μg/day) together with antithyroid drug. The extent of eye involvement was assessed by physical examination, exophthalmometry (Hertel), visual acuity and orbital ultrasonography. The exophthalmometry measurements were carried out by one observer using one Hertel exophthalmometer to minimize the error in the measurements. Orbital ultrasonography was performed and the muscle index was measured to evaluate any change in the extracocular muscles, as reported elsewhere (Yamamoto et al., 1979).

Steroid therapy
a. Systemic steroid therapy.
Prednisolone, 100 mg/day, was prescribed in 3 patients for 2 weeks and the outcome of the therapy was judged 4 weeks after the therapy.
b. Retrobulbar injection of steroid.
Three patients were treated with retrobulbar injection of 20 mg of methylprednisolone acetate (depot type), once a week for 4-5 weeks. The retrobulbar injections were performed at closer intervals than those reported by Garber (1966). The outcome of the therapy was followed for 4 weeks after the last retrobulbar injection.

Supervoltage orbital radiotherapy
The radiotherapy was given to 9 patients by the method of Donaldson et al. (1973). The outcome of the therapy was judged after 4 weeks, and the effect on proptosis and diplopia was further followed for at least 6 months.

Plasmapheresis
Two patients with Graves' disease and malignant exophthalmos were treated by plasmapheresis. Four sessions of plasma exchange were performed by using a Hemonetic cell separator. About 5 L of plasma was exchanged for the same volume of normal fresh-frozen plasma and saline. Immunosuppression was also carried out with prednisolone (60 mg/day) in one patient. The cell separator enabled us to draw blood, separate plasma fraction and return the cellular fraction of blood with normal fresh-frozen plasma, continuously. Blood was drawn at a rate of 30-40 ml/min and 1 L of plasma was exchanged within 90 min.

Thyroxyne replacement therapy
Three patients whose ophthalmopathy deteriorated during the antithyroid therapy or after subtotal thyroidectomy, were given thyroxine replacement. Soon after the development of double vision and/or ocular pain, the patients were put on thyroxine replacement (100–150 μg/day).

Evaluation of the effect of the therapy
The effect of the therapy was judged by scoring the ophthalmopathy index (Donaldson et al., 1973) using the classification of the signs and symptoms of exophthalmos of Werner (1977). Scores for the proptosis were modified to fit the degree of proptosis in Japanese, which is less prominent than that in Caucasians (16–19 mm=1; 19–22 mm=2; >22 mm =3). The overall response was also judged by the criteria for clinical evaluation of effects based on the classification of Donaldson et al. (1973).

Results
All patients subjected to this series of treatments were euthyroid under antithyroid

<table>
<thead>
<tr>
<th>Table 1. Clinical assessment of the therapy.</th>
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<tr>
<td><strong>Patient number</strong></td>
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<td>---------------------</td>
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<tr>
<td>Steroid Therapy</td>
</tr>
<tr>
<td>Steroid Therapy &amp; Radiation</td>
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<tr>
<td>Plasmapheresis &amp; Radiation</td>
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<tr>
<td>Radiation</td>
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<tr>
<td>Thyroxine replacement</td>
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<td><strong>TOTAL</strong></td>
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Numbers in the table present the number of the patients.
The overall responses were judged by the criteria for clinical evaluation of Donaldson et al. (1973).
drug treatment or after subtotal thyroidec- 
tomy. In 11 patients, ophthalmopathy had deterio-
rated during the antithyroid therapy regimen. The 
overall clinical responses are presented in Table 1. 
Excellent or good results were observed in 61.5% of 
the patients and none became worse. One 
patient who received systemic steroid therapy 
achieved excellent results. The proptosis 
improved by 3 mm (from 18 mm to 15 mm) 
along with marked amelioration in the soft 
tissue involvement. His clinical remission 
continued for more than 3 years after ter-
mination of the steroid therapy. All cases 
who received steroid therapy showed some 
 improvement in ocular pain, chemosis and 
diplopia within 3 or 4 weeks of therapy. The 
ophthalmopathy index decreased signifi-
cantly after therapy (before, 4.7±1.5; 
after, 2.5±1.5; p<0.005) but the Hertel 
readings did not improve during therapy 
(before, 21.5±1.7 mm; after 21.0±1.7 mm; 
N.S.). The muscle index also was not 
changed by therapy (before, 8.1±1.8; after, 
7.8±1.8; N.S.). Five cases whose proptosis 
was not improved by steroid therapy were 
given successive radiation treatments. Two 
patients were treated with plasmapheresis 
for the acute deterioration of proptosis and 
the ulceration of the cornea. The clinical 
course of one patient is demonstrated in 
Figure 1. Plasmapheresis was characterized 
by an immediate effect. At the end of the 
fourth session of plasma exchange, the 
proptosis decreased by 2 mm and ulceration 
of the cornea recovered. Double vision 
also improved subjectively. The ophthalmopathy 
index decreased from 7 to 2. During 
tapering of prednisolone, however, 
double vision and chemosis were aggravated, 
with a noticeable increase in the proptosis. 
The patient was readmitted and plasmapheresis 
was restarted. After 3 sessions of 
plasmapheresis, chemosis disappeared, and 
double vision and exophthalmos were im-
proved. In another case using plasmapheresis 
without simultaneous immunosuppression 
therapy, the proptosis did not change. Chemosis and ocular pain improved 
2 weeks after the plasma exchange and 
the ophthalmopathy index decreased from 
6 to 4. These 2 patients received subse-
quently orbital radiotherapy for the relapse. 
Orbital radiotherapy was given to 9 
patients. Five patients had previous steroid 
therapy and 2 had prior plasmapheresis. 
The remaining 2 patients were judged not 
to be appropriate for steroid therapy be-
cause they had had manifestations of ophthalmopathy for more than 3 years. Of 
The same results were obtained from the examines of
changes in muscle index during the orbital radiation therapy (Table 2). The patients who had been treated within 12 months of deterioration showed a better response to the therapy than those who had ophthalmopathy for a longer period. The effect of radiation therapy on the symptoms of the orbital soft tissue involvement (ocular pain, chemosis and epiphora) appeared after 3 or 4 weeks of therapy. On the other hand, the improvement in proptosis appeared 3-7 months after therapy. Three patients whose ophthalmopathy deteriorated during the antithyroid therapy or after subtotal thyroidectomy were immediately treated with thyroxine replacement. Two were under antithyroid drug therapy and one had prior subtotal thyroidectomy. Extraocular muscle enlargement was observed by echogram. Figure 2 indicates the clinical course of a patient whose diplopia began after subtotal thyroidectomy. A high TSH level was present for 10 months. The patient complained of diplopia and thyroxine, 100 μg/day, was prescribed. Diplopia worsened during 2 months of thyroxine therapy and

Table 2. Changes in proptosis and the muscle index after orbital radiation therapy.

<table>
<thead>
<tr>
<th></th>
<th>Hertel reading (mm)</th>
<th>Muscle index</th>
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<tr>
<td><strong>A. Nine patients who</strong></td>
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<tr>
<td><strong>received radiation</strong></td>
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<tr>
<td><strong>therapy.</strong></td>
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<tr>
<td>Before therapy</td>
<td>21.3±1.7 p&lt;0.05</td>
<td>7.6±1.9 N.S.</td>
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<tr>
<td>After therapy</td>
<td>20.1±1.5</td>
<td>7.3±1.8</td>
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<td><strong>B. Five patients</strong></td>
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<td><strong>showing clinical</strong></td>
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<tr>
<td><strong>improvement after</strong></td>
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<tr>
<td><strong>radiation therapy.</strong></td>
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<tr>
<td>Before therapy</td>
<td>21.5±1.7 p&lt;0.005</td>
<td>8.1±1.8</td>
</tr>
<tr>
<td>After therapy</td>
<td>19.2±1.8 p&lt;0.02</td>
<td>6.9±1.7</td>
</tr>
<tr>
<td>Graves' disease patients</td>
<td>16.7±2.9 p&lt;0.05</td>
<td>5.2±1.0</td>
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<td>without infiltrative</td>
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<tr>
<td>ophthalmopathy (11)</td>
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The muscle index was calculated as indicated in Materials and Methods.
the replacement dose was increased to 125 µg/day. Diplopia improved when the serum TSH level decreased to the undetectable range. During the course of treatment, there was no significant change in proptosis.

The correlation of changes in Hertel reading and the muscle index during the therapy of malignant exophthalmos was analyzed. The 2 parameters were significantly correlated ($r=0.728$, $p<0.001$). In 6 patients with malignant exophthalmos, the 2 parameters changed in parallel (Figure 3).

### Discussion

With the therapeutic regimens used in this study, 84.6% of the patients showed some improvement, but the effect was mostly on the symptoms of orbital soft tissue involvements. Donaldson et al. (1973) reported the efficacy of orbital radiotherapy in 91.3% and Corvington et al. (1977) in 71.4% of patients. Recently, however, Teng et al. (1980) reported somewhat disappointing results. Only 35% showed some response and 25% improved minimally. Only 25% of the patients had improved proptosis. In our study, the effects on proptosis were also rather unsatisfactory. In six patients (46.2%) proptosis decreased by 2.3 mm on the average. It should be emphasized that they still had noticeable exophthalmos as compared to Graves' disease patients without infiltrative ophthalmopathy. It is sometimes observed that the symptoms of Graves' ophthalmopathy naturally improve during antithyroid drug therapy. We previously compared the extraocular muscle change in a group of untreated patients and that of treated patients (Yamamoto et al., 1979). The extraocular muscle of euthyroid patients on antithyroid drugs was similar to that in untreated patients. Therefore, we felt that the significant decrease in proptosis and muscle index after orbital radiotherapy was a valid effect of the treatment. For regression of proptosis, radiation therapy is the
most beneficial among the therapeutic regimens used in this study, especially in patients who received the treatment shortly after the development of malignant exophthalmos. The effect of the radiation can be divided roughly into 2 categories, namely the early effects and the delayed effects. The effect on the soft tissue changes appeared 3-4 weeks after radiation therapy, while the effect on the proptosis appeared after 6 months. An early appearance of the effects of radiation therapy has been reported (Donaldson et al., 1973; Corvington et al., 1977), but in these reports no description of the effect on the proptosis is given. Steroid therapy was effective on the symptoms of orbital soft tissue involvement such as ocular pain, epiphora, chemosis and lid swelling. The results appeared within 3-4 weeks of the therapy. As for the proptosis, however, the steroid therapy was not effective except in one patient. Plasmapheresis showed a clear and immediate effect in a patient treated with prednisolone. The effect was characterized by an immediate improvement in proptosis. Since the response was transient, the therapy was thought to be beneficial for acute complications of the disease such as optic neuropathy, aggravation of exophthalmos, and ulceration of the cornea. Permanent remission should be maintained by simultaneous (or successive) steroid therapy or orbital radiation therapy. The potential risk of exacerbation of ophthalmopathy after thyroid ablative therapy has been emphasized. It has been proposed that this is due to sudden release of thyroid antigen. In this study, 11 patients (84.6%) had deterioration of ophthalmopathy during the antithyroid treatment. In the early stage of the deterioration, thyroxine replacement was useful for ameliorating diplopia or ocular pain. No effect of replacement therapy was observed on proptosis.

We have suggested the utility of the muscle index in diagnosis and following the progress of exophthalmos in Graves' disease (Yamamoto et al., 1979). The validity of the parameter is proven in this study by the positive correlation between the changes in the muscle index and Hertel readings during therapy of malignant exophthalmos. By measuring the index, an objective judgement of the effect of the therapy becomes possible.

In conclusion, radiation to retro-orbital space is the most beneficial therapy for improving diplopia and proptosis. It should be performed in the early stage of deterioration of ophthalmopathy to get a satisfactory effect. Orbital echography is useful in detecting progressive changes in the retro-orbital space.

Acknowledgment

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References


orbital irradiation for Graves' ophthalmopathy. 