Initial experience with gamma knife surgery for endocrine ophthalmopathy

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Object. The aim of this study was to evaluate both the effectiveness and safety of the treatment of endocrine ophthalmopathy with gamma knife surgery (GKS).

Methods. Five patients were included in a prospective study designed to assess the results of GKS of endocrine ophthalmopathy secondary to Graves disease. All the patients completed a 2-year follow-up period. During this period, the patients were evaluated both clinically and by means of additional methods, including computerized tomography and magnetic resonance imaging studies. The minimum dose delivered to the 50% isodose line was 6.5 Gy in all the patients.

In all cases, a clinical improvement was observed. The best effect was seen in symptom regression related to soft-tissue involvement. No treatment-related side effects were detected.

Conclusions. In light of the results obtained the authors consider that GKS may be a safe and effective way to treat endocrine ophthalmopathy.

KEY WORDS • gamma knife surgery • endocrine ophthalmopathy • Graves disease

In the year 1835, Robert Graves described for the first time the association between thyrotoxicosis, goiter, and exophthalmos. This syndrome came after further experience and study to include lagophthalmos, chemosis, lid lag, ophthalmoparesis, periorbital edema, and suffusion of the episcleral vessels.

Pathogenesis of Endocrine Ophthalmopathy

Endocrine ophthalmopathy has been recognized as an autoimmune disorder, the cause of which is not clearly known. The cause might be related to some complication of Graves disease, which may produce an antigen leading to a reaction between the thyroid gland and the extraocular eye muscles. Histologically, some inflammatory lymphocytic cell infiltration is observed with associated edema at the level of the medial and inferior rectus muscles, and to a lesser degree, of the superior rectus muscle. Clinically, the expression of this condition varies with symptoms ranging from eye redness to a significant enlargement of the muscle that in turn leads to the forward displacement of the eyeball, producing ophthalmoplegia, keratitis, and even optic neuropathy with a progressive loss of vision. Between 50 to 90% of patients with Graves disease develop endocrine ophthalmopathy. This condition is not always symptomatic and progressive; thus it does not always require treatment.

Clinical Material and Methods

Five patients with endocrine ophthalmopathy were treated with GKS prospectively between August and December 2001. All have been followed up for 2 years. Previous approval from the ethics committee and informed consent had been obtained. All the patients had advanced disease and had been referred after failing to respond to treatment with steroid agents. Moreover, all of them had previously been treated for thyrotoxicosis. The clinical and biochemical thyroid status before GKS was considered euthyroid in four patients (80%) and hyperthyroid in one patient (20%).

Four patients (three women and one man) underwent unilateral treatment, whereas one underwent bilateral treatment. The average age was 56 years (range 36–70 years).

Once the stereotactic frame was fixed, computerized tomography and magnetic resonance images were acquired both before and after the administration of intravenous contrast material. Ocular fixation to immobilize the target was not necessary because eye immobilization is a feature of
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this condition. The immobilization was checked by means of imaging studies performed both pre- and postoperatively; however, in all cases, a stenopeic disc was fixed to the eyeball to be treated.

Leksell GammaPlan (version 5.31; Elekta Instrument AB, Stockholm, Sweden) planning system was used for dose planning. The relevant muscular thickening was defined as the target. The dose indicated for the lesion margin was 6.5 Gy placed on the 50% isodose line at a maximum dose of 13 Gy. The mean dose delivered was 8.5 ± 2.1 Gy.

In no case was the dose delivered to the optic nerve higher than 4 Gy. For the unilateral lesions 22, 20, 17, and 15 isocenters were used and 32 for the bilateral treatment (Fig. 1). In all cases, some plugging was used to adapt the radiation volume to the target volume (Fig. 2). The mean target volume was 1.3 cm³ (range 0.5–3.6 cm³). During the 2-year follow up, all the patients were clinically evaluated by a neurosurgeon and an ophthalmologist on a weekly basis during the first 2 months and then every 30 days during the 1st year. After the 1st year, control evaluations were performed every 3 months until the end of the study. Imaging studies were performed within 30 days of the procedure and then every 4 months during the 1st year. Another control evaluation was performed at the end of the study.

<table>
<thead>
<tr>
<th>Target Point 12 (Shot A12)</th>
<th>Collimator Helix</th>
<th>Coordinate s.x.z</th>
<th>Gamma Angle</th>
<th>Plugging</th>
<th>Treatment Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>109.2, 186.3, 137.0</td>
<td>120°</td>
<td>Auto</td>
<td>4 Gy</td>
<td></td>
</tr>
</tbody>
</table>

This shot is to be treated with the patient in the PRONE position. Set the gamma angle according to the normal procedure.

Effective plug pattern:
- A8-A12 A12-A41
- R1-R12 R12-R14 R14-R16 R16-R18
- C1-C5 C5-C19 C19-C34 C34-C36
- D1-D14 D14-D17

Fig. 2. GammaPlan schematic: some of the radiation was plugged as shown by the black circles in this diagram. This permits a fine tuning of the radiation distribution, which is needed in such a delicate anatomical situation.

Fig. 3. Graph showing the difference between the degree of exoophthalmos by using the Hertel method before and after treatment.
Results

Even at the first clinical evaluation 1 week after the procedure, symptoms and acute inflammatory signs had improved. Also, decreases in chemosis, conjunctival edema, and photophobia were observed in all the patients. The intraocular foreign body sensation disappeared and was the symptom with the best improvement recorded. During the period between 60 and 90 days after GKS, images revealed a decrease in the volume of the muscles treated. Consequently, on clinical evaluation an improvement in proptosis was observed, which was considered a 2-mm or greater decrease by using the Hertel method. Recovery of visual acuity then followed, and intraocular pressure went down. The decrease in proptosis and intraocular pressure was associated with an improvement in lacrimation. Severe ophthalmoplegia with manifest strabismus with a long symptomatic history showed the least improvement, occurring in only one patient (20%). All the results obtained during the 1st year were maintained until the end of the follow-up period. No side effects due to radiation were observed. It would seem that GKS is precise enough and safe enough at an apparently biologically effective dose to spare surrounding tissues (Figs. 3–7).

Discussion

According to the theory of Topliss and Volpe, abnormal clonal proliferation of plasma cells is not prevented by abnormal and malfunctioning suppressor T lymphocytes. A consequence of this proliferation could be migration of abnormal plasma cells to the orbit, with the production of antibodies that form antigen–antibody complexes, coating the extraocular muscle fibers with a secondary inflammatory reaction. The resulting muscle enlargement could lead to congestion of the orbital contents and promote the symptoms described. The radiobiological effectiveness of a low
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dose of radiation would not be surprising in view of the influence of radiation on both T-cell subsets and fibroblasts. The inactivation of T cells and other mediator cells stimulates antiinflammatory activity by reducing the number of lymphocytes and normalizing pH levels. When exposed to radiation, fibroblasts exhibit a decrease in their activity and also a decrease in glycosaminoglycan release, resulting in an antiedematous action. All this has been clearly shown in several studies, which reported successful results in the use of fractionated external-beam radiation. The risk factors leading to the development of ophthalmopathies in Graves disease have been investigated in recent years, mainly in relation to the different treatment modalities used in thyrotoxicosis. Tallstedt and coworkers reported a significant increase in the risk of ophthalmopathy development or worsening of existing ophthalmopathies in patients treated with radiiodine compared with those treated surgically and with antithyroid agents. One hundred seventy-nine patients were included in their study: 13% of those treated surgically or with antithyroid agents and 33% of those treated with radiiodine therapy either developed ophthalmathy or their existing ophthalmopathies grew worse.

In brief, although ophthalmopathy seems to be independent of the thyroid status and can occur in euthyroid patients, there is enough evidence to show that it is more likely to occur in patients who develop hypothyroidism after undergoing radiiodine therapy.

This small study indicates that GKS may well be more effective and could have a more significant impact during the early and inflammatory stages of the disease, considering that in cases of severe ophthalmoplegia corrective surgery may be required.

Conclusions

It appears that GKS has had a beneficial clinical effect on the ophthalmopathy in Graves disease in six eyes in five patients, all of which had severe disease. There were no regressions of beneficial effect nor GKS-related complications in a follow-up period of 2 years. The effect on severe well established ophthalmoplegia was disappointing so that the treatment might work even better at an earlier stage of the disease.

References


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