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## **Radiation optic neuropathy after external beam radiation therapy for acromegaly: report of two cases**

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## Abstract

For diagnosing radiation optic neuropathy (RON) ophthalmological and imaging data were evaluated from 63 acromegalic patients, irradiated between 1967 and 1998. Two patients developed RON: one patient in one optic nerve 10 years and another patient in both optic nerves five months after radiation therapy. RON is a rare complication after external beam radiation therapy for acromegaly, which can occur after a considerable latency period.

## Introduction

Acromegaly is an uncommon disease, mostly caused by a growth hormone (GH)-secreting pituitary adenoma. Surgery, drug therapy with somatostatin analogs and external beam radiation therapy are currently the available treatment options<sup>8</sup>. Postoperative radiation therapy is performed to reduce the time span of medical treatment, to normalize GH hypersecretion, and to prevent regrowth of residual tumour<sup>10</sup>.

In the past decades, scattered reports on radiation optic neuropathy (RON) have appeared in the literature<sup>4</sup>. RON is usually defined as a sudden and profound irreversible vision loss due to damage of the optic nerves or damage of the chiasm caused by radiation therapy<sup>7</sup>. The aim of this retrospective study is to describe the occurrence of RON in a cohort of patients treated with radiation therapy for a GH-secreting pituitary adenoma.

## Materials and Methods

During the period 1967-1998, 80 patients with acromegaly were diagnosed at the University Hospital Groningen, The Netherlands. The diagnosis of acromegaly was based on the typical clinical features of acral enlargement and soft tissue swelling and was confirmed by appropriate laboratory tests. In all operated patients histological evaluation of the specimen confirmed the presence of a GH-producing pituitary adenoma.

In 1999 and 2000, a retrospective investigation was performed. The ophthalmological, surgical and radiation therapy data were reviewed. The time period 1967-1998 was chosen because data before 1967 were frequently incomplete. To be included in the present survey, time of follow-up had to be at least 18 months. The ophthalmological data obtained before treatment were available in all but two patients and after radiation therapy from all patients.

Of these 80 cases, 63 patients, who were treated with external beam radiation therapy, were included in our survey. External radiation therapy was mostly performed at the University Hospital Groningen ( $n = 56$ ), but also in 2 other regional institutions ( $n = 7$ ), where equivalent radiation therapy schedules were applied.

Before 1977 the neurosurgical procedures were craniotomies only. Since 1978 the transsphenoidal approach was the preferred method.

Visual acuity was measured with a Snellen acuity chart. A visual acuity less than 0.8 was defined as impaired. Visual fields were obtained with Goldmann kinetic perimetry. The visual field data ( $n = 1195$ ) of all patients at diagnosis, after neurosurgery and/or radiation therapy were retrospectively reviewed by one neuro-ophthalmologist.

We diagnosed RON using the criteria by Kline et al. and Parsons et al.<sup>7,9</sup>:

- Irreversible visual loss with visual field defects, indicating optic nerve or chiasmal dysfunction.
- Absence of visual pathway compression due to recurrence or progression of tumour, radiation-induced neoplasm, arachnoidal adhesions around the chiasm, radiation retinopathy or any other apparent ophthalmological disease.
- Absence of optic disc edema.
- Optic atrophy within 6 - 8 weeks after onset of symptoms.

Evaluation of RON was performed by review of visual field, visual acuity and fundoscopic examinations in combination with imaging of the sellar region.

The time span of follow-up was defined by the period between the first day of radiation therapy and the last ophthalmologic examination.

## Results and Discussion

Median age at the start of radiation therapy was 43 years (range 19-64 years). Twenty-eight patients were males (44%) and 35 patients were females (56%). Fourteen patients were treated with radiation therapy alone. Forty nine patients were treated with a combination of radiation therapy and surgery of whom 40 patients had one, five patients had two and one patient had three operations before radiation therapy. Two patients underwent surgery after radiation therapy. One patient had radiation therapy in between two pituitary operations. Median follow-up time in the radiation therapy group was 84 months (range 18 - 250 months).

Total radiation therapy dose ranged from 45 to 55.5 Gy (median dose 49.5 Gy). Median overall treatment time was 36 days (range 31-54 days). The daily fraction size varied from 1.8 to 2.1 Gy in 55 patients (median dose 1.8 Gy). In six patients the radiation therapy course was initiated with gradually increasing doses between 1 Gy and 2 Gy daily. From two patients only the total dose was known, but we assume that they were treated with an increasing daily dose as just mentioned, which was standard between 1967 and 1974. The most common dose and fractionation scheme used was 45 Gy in 1.8 Gy daily fractions ( $n = 27$ ; 43%), mainly performed in the time period 1985-1998. Fifty Gy in 2 Gy daily fractions, mainly performed in the time period 1974-1984 was administered to 20 patients (32%). Eleven patients received a total dose greater than 50 Gy; ten of them had been irradiated before 1981. In all patients all radiation treatment fields were given every treatment day.

In the time-period 1969-1978 the betatron with energy 18 MV HVD 17 mm PB was used in 13 patients; a five- or seven-field technique was used with standard field sizes of 4 by 4 cm. Three patients were treated with a cobalt source, energy 1.25 MV HVD 11 mm PB, a four-field technique was used twice and a combination of an opposed lateral field

technique followed by a three-field technique was used once. Treatment fields varied between 4 and 5 cm in lateral or cranio-caudal dimension. From 1979 onwards patients were treated on linear accelerators with 4MV photons (n = 2), 6 MV photons (n = 20), 8 MV photons (n = 24) and 10 MV photons (n = 1). A two-field opposed lateral technique was used in seven patients, a three-field technique in 12 patients, a rotation technique in one patient, a five-field technique in 11 patients, a six-field technique in one patient and a combination of above mentioned techniques in 15 patients; most of the time a combination of opposed lateral fields followed by a five-field (n = 11) or a three-field technique (n = 3). In the time period 1979-1989 the treatment plan was normalised on the encompassing isodose, afterwards according to ICRU<sup>11</sup>. Treatment-field dimensions varied between 3 and 6 cm.

RON was diagnosed in two of the 63 irradiated patients (3.2%, 95% CI: 0.3 - 11.2%). In one patient RON was unilateral (case 1) and in the other patient RON was bilateral (case 2).

### Case 1

A female, aged 52 years, underwent pituitary irradiation in 1969, with a total dose of 55.5 Gy given in 54 days, with an assumed daily dose 1 to 2 Gy, with 18 MV betatron photons and a seven-field technique for a GH-producing pituitary adenoma. At diagnosis of acromegaly and within the first ten years after radiation therapy no visual deficits were reported. In 1979 she suffered sudden visual loss in the left eye decreasing to light perception only. On fundoscopy of the left eye, the optic nerve was atrophic. Goldmann kinetic perimetry showed a central scotoma; the visual functions of the right eye were normal. A CT-scan of the pituitary fossa showed a residual intrasellar pituitary mass without suprasellar extension.

Subsequent CT-scans also did not reveal suprasellar mass; she declined to undergo an MRI.

### Case 2

The second patient, a 42 year old female, underwent a frontal craniotomy in 1968 because of a suprasellar pituitary adenoma. The optic nerves and the optic chiasm were embedded in the tumour, but pre- and postoperatively the visual acuity of both eyes was normal and there were no visual field defects. Six months later radiation therapy was started, because of persistence of GH hypersecretion. The radiation schedule was 50 Gy in 2 Gy daily fractions in 42 days. Eight megavolt photons and a three-field-technique were used. Five months later, she complained about progressive visual loss, occurring within a few weeks. At ophthalmological examination the visual acuity of the left eye was 0.1 and was accompanied by a temporal hemianopsia. The visual acuity of the right eye was 1.0 with an altitudinal visual field defect in the upper quadrant. On fundoscopy

there was bilateral optic atrophy. The visual field defect of the left eye did not change, but the visual acuity deteriorated gradually in a time span of 2 years to 1/60. The visual field defects of the right eye worsened in 1983 and 1988. In this eye the visual acuity changed to 0.7 in 1992 and 0.5 in 1995.

A pneumoencephalogram made in 1979 showed limited suprasellar extension of the pituitary adenoma with the optic system well demarcated in the suprasellar air thus excluding tumour recurrence. This finding strongly suggest that the visual deterioration in the left eye was due to radiation treatment. We assume by reviewing of all ophthalmologic data and exclusion of other causes, that the gradually worsening of vision in the right eye is also due to RON.

In the present series, two out of 63 irradiated patients (3.2%) developed RON. A total radiation dose greater than 50 Gy and/or a radiation fraction size greater than 2 Gy are suggested to be risk factors for RON<sup>1,9</sup>. One of the presently reported cases had a total radiation dose of 50 Gy and a radiation fraction size of 2 Gy. This would suggest the presence of other risk factors, associated with the development of RON after radiation therapy in GH-secreting pituitary adenoma. Apart from the probable risk attributable to vascular compromise<sup>6,9</sup>, GH-secreting pituitary adenoma as such may confer an increased risk for RON development as previously suggested<sup>1-3,5</sup>. In case 2 of the present series the optic nerves and optic chiasm were embedded in the tumour, which may have been contributed to the development of RON.

It is generally proposed, that most cases of RON occur within 18 months after radiation therapy<sup>7</sup>. Case 1 of the present series well illustrates, that late development of RON can occur, indicating that the clinician should remain alert of this complication, even many years after radiation therapy.

RON is a rare complication after external beam radiation therapy for acromegaly, which may occur after a considerable latency period.

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