5 Radiation optic neuropathy after external beam radiation therapy for acromegaly

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Introduction

Acromegaly is an uncommon disease, mostly caused by a growth hormone (GH)- secreting pituitary adenoma. Its incidence has been estimated at 2.8 - 6 cases per million and its prevalence at 38 - 68 cases per million[2,10,64].

A GH-secreting pituitary adenoma does not only lead to clinical signs and symptoms, like acral enlargement and soft tissue swelling, but may also be accompanied by visual field defects and acuity loss caused by tumour compression on the optic nerves or chiasm, often seen in combination with pituitary hormone insufficiencies.

Surgery, drug therapy with somatostatin analogs and external beam radiation therapy are currently the available treatment options[61]. External beam radiation therapy is available since the beginning of the 20th century[12,35]. It became clear, however, that radiation therapy alone often results in insufficient biochemical control, which means a decline but not a normalisation of GH hypersecretion[3,4,24,29,56]. Consequently, surgery became the initial treatment of choice. According to some experts drug therapy may be the first treatment of choice for selected patients[61]. Postoperative radiation therapy is performed in many centres to reduce the postoperative time span of medical treatment, to normalize remaining GH hypersecretion, and to prevent regrowth of residual tumour[75].

Radiation Optic Neuropathy (RON) was for the first time reported by Forrest et al. in 1956[30]. They defined RON as a sudden and profound irreversible vision loss due to damage of the optic nerves or damage of the chiasm caused by radiation therapy.

Kline et al. and Parsons et al. defined the following criteria for diagnosing RON[49,65]: (a) irreversible visual loss with visual field defects, indicating optic nerve or chiasmal dysfunction; (b) 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; (c) absence of optic disc edema and (d) optic atrophy within 6 - 8 weeks after onset of symptoms.

In the past decades many reports on RON have appeared in the literature. The last review of RON in acromegaly was published by Eastman et al. in 1992[25]. The radiation dose level for the occurrence of RON is not known. Moreover the dose-response relationship for RON has not been firmly established due to the small numbers of events in most series[46,65]. It has been suggested that the maximal steepness of the sigmoid dose-response curve for RON is between 50 and 60 Gy[46,65]. The occurrence of RON after doses as low as 45-50 Gy administered in fractions of 1.67 - 2 Gy seems to be a problem unique to patients with pituitary tumours, and probably reflects pre-existing optic nerve and chiasm compression and vascular compromise secondary to a mass effect or due to surgery[46,65].

Some authors propose that the optic system in acromegalic patients might be more sensitive to radiation damage compared to patients irradiated for non-functioning pituitary adenomas[5,6,13,39]. This may be caused by vascular and hormonal changes in relation to acromegaly[5], but this opinion is not uniformly accepted[23,25].

The purpose of this literature survey is to determine the incidence of RON in acromegaly, and to establish risk factors associated with its occurrence

Literature search and data analysis

The literature review was done, using Medline between 1966 and June 2002 and Embase between 1989 and 2002. Key words searched for were RON, acromegaly and radiotherapy as well as pituitary adenoma and radiotherapy. All papers that included acromegalic patients were checked for vision loss due to radiation therapy. The references retrieved by Medline and Embase were screened for other references, not found by using the above-mentioned key words.

To estimate the incidence of RON in acromegaly we only included cohort series of patients, in which RON was taken into consideration. In case of a cohort of all kind of pituitary adenomas, it was only included in Table 1 in case of a known number of acromegalic patients, in which it was clear how many patients suffered RON. To evaluate risk factors for RON development we included RON-patients from series in which radiation treatment data were available, as well as individual case reports. This present survey includes our own series of 63 patients of whom two developed RON[11].

Incidence of RON

As shown in Table 1, 25 of 1845 patients developed RON, yielding an incidence of 1.36% (95%CI: 0.94 - 1.89%). This figure is not significantly lower than that reported by Eastman et al., who calculated an incidence of 2.2% (95%CI: 1.53 - 3.17%) ($P = 0.10$)[25]. The incidence reported by Eastman et al. is likely to be overestimated, because they included single case reports of RON in their review[25]. Although the incidence of RON is low, it is considered a serious complication of radiation therapy. It is therefore of interest to identify the severity of visual loss and the radiation treatment characteristics associated with its occurrence.

Table 1 Incidence of RON in reported series of acromegalic patients

Reference	Number of patients	Total radiation dose (Gy)	Fraction size(Gy)	Number of RON cases	Treatment period
[73]	31	35-50	1.8	1	1942-1959
[34]	53	na	na	1	1932-1960
[20]	22	na	na	0	1938-1958
[50]	7	40-45	2.5	0	na
[27]	34	40	2	0	1940-1963
[33]	30	45	1.8	0	na
[56]	28	29.5-66	na	0	1946-1970
[45]	12	35-50	na	0	na
[51]	29	40-50	2	1	1957-1971

[47]	12	na	na	0	na
[44]	10	35-37.5	2.2-2.35	0	na
[4]	10	55	2	0	na
[54]	25	16-80	na	0	1954-1975
[41]	6	45-50	2-2.5	0	1968-1973
[66]	19	44-76	2	0	1956-1972
[40]	18	40-60	na	1	1962
[5]	25	na	na	1	1952-1971
[6]	23	42-45	na	4	1961-1975
[24]	47	40-56	2-3	1	na
[9]	102	na	na	0	na
[17]	35	50	2	1	1967-1976
[8]	17	45-50	1.8-2	0	1971-1982
[16]	5	na	na	0	1971-1979
[48]	28	30-46	2	0	1950-
[31]	33	50-55	na	0	1974-1983
[82]	27	50	na	0	1974-1982
[13]	40	45-50	1.8-2.2	5	1957-1982
[29]	46	37.5	2.5	0	1947-1983
[7]	11	40-50	na	0	1977-1984
[83]	25	50	1.8	0	1968-1982
[81]	80	na	na	0	na
[70]	44	na	na	1	1970-1984
[58]	17	44.5-62	2	1	1971-1982
[59]	27	36-48	1.92-3.6	1	1962-1987
[53]	41	40-50	1.6-2	0	1978-1988
[1]	12	31-70	na	1	1958-1987
[23]	25	24-53.44	1.67-2.5	0	1956-1988
[57]	46	35-40	2.33-2.66	0	1970-1988
[75]	33	40	2	0	1964-1978
[78]	15	44-55	1.8-2.5	0	1967-1985
[77]	56	50	1.8	0	1972-1986
[32]	22	45-50.4	1.8-2	0	1965-1989
[71]	29	45.7-56	1-2.5	0	1961-1986
[36]	11	50	2-2.2	0	1980-1985
[19]	10	40.5-50.4	1.8-2.5	0	1976-1991
[22]	54	48	na	0	1972-1983
[18]	19	45-50.4	1.8	0	1986-1991
[84]	19	40-45	1.8-2.25	0	1973-1992
[63]	10	45-59.4	1.8-2	0	1980-1991
[79]	52	40-52	1.8-2.5	1	1972-1986
[76]	28	45-50	1.8-2	0	N(1973-1995)
[68]	132	na	na	1	1951-1996
[67]	32	47.4(45-54)	1.8(1.7-2)	0	1981-1999
[28]	67	53.6(40-75)	1.5-1.8	0	1969-1996
[37]	41	46-54	1.8-2.5	0	1948-1996
[21]	49	45.08±0.98	2	1	1960-2000
[11]	63	45-55.5	1.8-2.1	2	1967-1998
Total	1845			25	

na: not available

Severity of visual loss and latency of RON occurrence

When reviewing reported cases of RON in acromegalic patients in whom total radiation dose and fraction size are reported (Table 2) –using the abovementioned search method - it appears that in 24 of 32 patients, in whom visual loss was specified, RON was bilateral in 17 patients (71%) and unilateral in seven patients (29%). Visual acuity was less than 2/10 in 35 of 41 RON affected eyes.

It is generally proposed, that most cases of RON occur within 18 months after radiation therapy[49]. However, Table 2 shows that in eight of 30 patients (27%), RON developed more than 18 months after radiation therapy (median 12 months, range 5-120 months). Thus late development of RON can occur, indicating that the clinician should remain alert of this complication, even many years after radiation therapy.

RON in relation to radiation treatment characteristics

A radiation fraction size greater than 2 Gy and/or a total radiation dose greater than 50 Gy are suggested to be risk factors for RON in general[5,65]. As shown in Table 2, it appears that in 16 of 32 cases (50%) radiation fraction size was greater than 2 Gy and/or total radiation dose was greater than 50 Gy. Information with respect to minimum and maximum radiation doses according to ICRU 50/62 recommendations[80] within the treated target volume, that also encompass the optic system, was not available in most reports.

Other risk factors for RON development

Apart from the probable risk attributable to vascular compromise, GH-secreting pituitary adenoma as such may confer an increased risk for RON development as previously suggested[5,6,13,39]. Older age is another possible risk factor for RON[65]. In 27 of 32 cases, reviewed in Table 2, age was reported. In this series median age was 53 years, which is approximately 10 years older than the age reported at diagnosis of acromegaly[42], and than the median age of the presented cohort[11]. However, in general there is a lack of data in published series with respect to age in those patients who did and who did not develop RON. Therefore, it is not possible to draw definite conclusions about age as a risk factor for RON development.

Remarkably, as shown in Table 2, 20 of 23 patients (87, 95%CI: 66 - 97%), in whom gender was reported, were female, our two cases included ($P<0.001$ from an equal sex distribution). Since the occurrence of acromegaly is not increased in females[42] and it is unlikely that females are treated with radiation therapy more frequently than males, this would suggest that females are at an increased risk for the development of RON. To our knowledge a female predisposition for RON has not been reported earlier.

Pathogenesis and treatment

RON is essentially defined as a diagnosis by exclusion[49]. Although the pathogenesis of RON is unclear, its microscopic appearance would suggest an initial microvascular injury that results in perivascular inflammation, hyalinization, and fibrosis of vessel walls and also loss of endothelium and consequently infarction with reactive gliosis[49]. Using MRI with gadolinium, enhancement of the retro-orbital optic nerves and chiasm usually occurs, probably as a consequence of a disrupted blood brain barrier within the optic nerves[14,38]. This may be used to differentiate RON from optic neuritis due to demyelination. Therefore, this diagnostic approach is currently proposed to improve the diagnosis of RON[14,38]. A few months after the onset of RON the gadolinium enhancement of the optic nerves on MRI disappears[38].

Until now there is no effective treatment for RON[69]. The effect of high dose corticosteroids and of anticoagulants is unclear[69]. Hyperbaric oxygen therapy has also been used to treat RON, but its efficacy is uncertain[15,69].

Table 2 RON in acromegalic patients, in whom total radiation dose and radiation fraction size are available

Ref	Sex	Age at RON (yrs)	Operation	Total dose (Gy)	Fraction size (Gy)	Treatment time (days)
[72]	M	46	No	50	2	36
[72]	F	60	No	50	2	34
[5]*	na	na	Na	50	2.5	35
[6]*	F	58	Yes	42.4	2.83	22
[6]*	F	51	No	43.8	3.13	19
[6]*	M	53	Yes	Yttrium-90 45.2	3	18
[6]*	F	63	No	42.4	2.83	22
[55]	F	63	Yes	50	1.52	N
[55]	F	52	Yes	50	2	n
[17]*	na	na	na	55	2.2	40
[39]	F	64	No	42.5	2.8	21
[39]	F	63	No	42.5	2.1	28
[39]	F	50	No	42.5	2.8	21
[13]*	na	51	na	46	2	31
[13]*	F	51	N	45	1.96	31
[13]*	na	60	N	50	2	35
[13]*	na	51	na	50	2.17	38
[13]*	na	47	N	50	2	35
[59]*	F	68	No	40	3.33	28
[59]*	na	na	Yes	60	2	42
[69]	F	68	No	50	2	na
[1]*	F	50	No	40.42	1.55	35
[52]	F	33	na	49.5	na	42
[38]	F	65	Yes	45	1.8	na
[62]	F	61	No	45	1.8	35
[26]	M	38	Yes	50	2.38	36
[43]	na	na	No	50	2.5	na
[74]	F	54	Yes	56	2	38
[79]*	na	na	na	42.5	1.93	na
[21]	F	53	Yes	46	2	N
[11]	F	53	Yes	50	2	42
[11]	F	52	No	55.5	1-2	54

na: not available; F: female; M: male; N: normal ;R: reduced; OS: oculus sinistra/ left eye; OD: oculus dextra/ right eye; VA: visual acuity; Bl: blind; LP: light perception; HM: hand movements: FC: fingercounting
[ ]* these references are mentioned in Table 1 and Table 2, because an incidence was mentioned and in case of RON treatment characteristics were available.

Latency of RON (months)	Visual status at diagnosis	Visual status due to RON
6	N	OD:FC OS:2/20
8	N	OD:FC
15	N	OD:Bl OS:Bl
14	N	OD:HM OS:HM
13	N	OD:reduced vision OS:Bl
After external beam: 84	R	OD:HM OS:Bl
10	R	OD:Bl OS:Bl
11	Na	Visual loss not specified
19	N	Visual loss not specified
11	na	Visual loss not specified
8	N	OD:Bl OS:Bl
8	R	OD:FC OS:FC
9	N	OD:Bl OS:Bl
18	N	OD:Bl
12	R	OD:LP
10	N	OD:Visual loss not specified
12	N	OS:Visual loss not specified
84	N	OD:Bl OS:Bl
10	N	OD:Bl OS:Bl
na	na	Visual loss not specified
19	n	OD:FC OS:2/10
36	N	Visual loss not specified
12	N	Visual loss not specified
24	N	OD:VA2/7 OS:VA2/3
8	N	OD:Bl OS:Bl
9	N	OD:VA 0.3 OS:VA 0.1
na	na	Visual loss not specified
16	N	OD:LP OS:VA 0.4
60	na	OS:Visual loss not specified
9	na	Visual loss not specified
5	N	OD:VA 0.5 OS:VA 1/60
120	N	OS:LP

Conclusions

Our literature review suggests that RON occurs in 1.36% of patients with GH-secreting pituitary adenoma, treated with external beam photon radiation therapy. Assuming that in as much as 50% of reported cases, no risk factors related to radiation therapy were present, would suggest that other risk factors, including vascular compromise and GH-secreting pituitary adenoma itself, contribute to RON occurrence. RON may occur after a considerable latency period. A female preponderance for developing RON is suggested.

The current dose-fractionation policy in our department is 45 Gy in 1.8 Gy fractions for all pituitary adenomas if radiation therapy is indicated. To our opinion there is no benefit in applying a higher total dose in pituitary adenoma radiation treatment, because a dose-volume effect above 45 Gy is absent[60]. Taken into consideration that in 50% of RON cases radiation treatment characteristics are likely to contribute to the development of this complication, our treatment scheme could further decrease RON development.

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