TREATMENT OF PITUITARY DEPENDENT CUSHING'S SYNDROME WITH CLOSED STEREOTACTIC RADIOSURGERY BY MEANS OF $^{60}$Co GAMMA RADIATION

By
M. Thorén, T. Rähn, K. Hall and E. O. Backlund

ABSTRACT

Four patients with pituitary dependent Cushing's syndrome were treated with external irradiation to the pituitary using $^{60}$Co gamma irradiation given with a stereotactic technique. The size of the sella turcica was normal or slightly enlarged in all patients. The doses given varied between 7000 and 10 000 rad, and the observation time ranged between 14 and 20 months. Three of the patients showed complete clinical remission and one marked improvement. One patient developed ACTH insufficiency, while none developed insufficient secretion of other pituitary hormones. No complications of the irradiation were observed.

No therapy has hitherto been entirely satisfactory in Cushing's syndrome due to overactivity of the hypothalamic pituitary axis. Bilateral adrenalectomy has been the most commonly used one because of its immediate effect on the cortisol overproduction. The extensive surgery and the life-long replacement therapy with glucocorticoids and often mineralcorticoids, which is necessary in these subjects, are detrimental to the procedure. Furthermore, it will not eliminate the underlying pathology, and will leave the patient with the risk of subsequently developing hyperpigmentation and a pituitary tumour, i.e., Nelson's syndrome (Nelson et al. 1960). Although the incidence of Nelson's syndrome after bilateral adrenalectomy seems to be reduced when combined with radiation therapy to the pituitary (Orth & Liddle 1971) the patient is still at risk (Wild et al. 1973).
Treatment directed to the pituitary gland itself would therefore be rational. Various techniques for radiation therapy and surgery have been employed. Conventional radiotherapy has few complications but the dose that can be given is limited to 4500 to 5000 rad, which has failed to control the disease in a significant number of patients. Stereotactic technique allows irradiation with better precision and, therefore, higher doses can be administered to the hypophysis.

We now report on our first four patients with pituitary dependent Cushing’s syndrome treated by stereotactically directed gamma radiation from $^{60}$Co.

MATERIAL AND METHODS

The material comprised 1 male and 3 female patients with pituitary dependent Cushing’s syndrome (Table 1). All four had the classical symptoms and clinical features of hyperadrenocorticism. The duration of the disease was more than 10 years in 1 patient who also demonstrated severe osteopenia with fractures and periods of mental depression. The disease was of a shorter duration in the other 3 patients – 1 to 3 years. They all had hypertension.

In all the patients there was an absence of normal circadian rhythm of plasma cortisol, increased excretion of urinary cortisol, and insufficient suppression of glucocorticoid production after dexamethasone administration with the classical dexamethasone test (Liddle 1960). Suppression of urinary cortisol with higher doses of dexamethasone (Liddle 1960) and a rise of 17-hydroxylated steroids in the urine after metyrapone administration (Liddle et al. 1959) demonstrated pituitary dependency. Furthermore, the patients exhibited an exaggerated response of plasma cortisol after ACTH administration.

Table 1.

Data including the neuroradiological findings in 4 patients with pituitary dependent Cushing’s syndrome treated with pituitary gamma lesion.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age at treatment (years)</th>
<th>Sex</th>
<th>Duration of the disease (years)</th>
<th>X-ray of the sella turcica</th>
<th>Orbital phlebography</th>
<th>Pneumoencephalography</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>40</td>
<td>female</td>
<td>≥ 3</td>
<td>normal</td>
<td>technically unsatisfactory</td>
<td>partially empty sella</td>
</tr>
<tr>
<td>B</td>
<td>60</td>
<td>male</td>
<td>≥ 3</td>
<td>slightly enlarged</td>
<td>normal</td>
<td>partially empty sella</td>
</tr>
<tr>
<td>C</td>
<td>56</td>
<td>female</td>
<td>≥ 10</td>
<td>rounded shape, normal size</td>
<td>normal</td>
<td>partially empty sella</td>
</tr>
<tr>
<td>D</td>
<td>44</td>
<td>female</td>
<td>≥ 1</td>
<td>rounded shape enlarged</td>
<td></td>
<td>partially empty sella</td>
</tr>
</tbody>
</table>
As seen from Table 1, the sella turcica was normal or only slightly abnormal in size or shape. All the patients had partially empty sella which is common in patients with hormone producing intrasellar tumours (Brismar et al., subm. for publ.).

Three to four months after treatment the patients were again examined with the single dose dexamethasone suppression test with ACTH stimulation (Thorén et al. 1975). In addition, urinary cortisol excretion, diurnal rhythm of cortisol, thyroid function, TRH-test, LH-RH-test, serum levels of prolactin, somatomedin, testosterone and/or oestradiol were measured. If not in remission at the first re-examination, the patients were re-investigated after another 2 months. They were then observed after 1 year and then at least every half-year, when tests for cortisol excretion, thyroid and gonadal functions were performed.

**Radiation technique**

The radiation technique will be described in detail elsewhere (Råhn et al., subm. for publ.), hence we present here a brief summary.

A modification of the gamma unit described by Leksell (1971) was used for the irradiation. The unit was designed for the purpose of producing minute spherically-shaped lesions in the brain to treat tumours and vascular malformations. The lesion is induced by collimated beams from 179 $^{60}$Co sources distributed within a hemispherical sector. The beams are radially directed towards the centre of the unit at which the target point in the gland has to be positioned.

By changing the collimators, the geometric cross-section of each beam can be altered from 8 mm to 14 mm to match the size and shape of the pituitary.

The irradiation was given in one single session and the individual doses varied between 7000 and 10,000 rad. The irradiation time with this technique was 4 to 5 min per 1000 rad. The dose gradient is very steep, permitting a high dose in the target point while the adjacent structures receive much lower doses. The dose to the optic tract is less than 10% of the dose in the target point when it is placed in the centre of the adenohypophysis and a total dose distribution as in Fig. 1 can be obtained.

The stereotactic localization of the pituitary, the determination of the co-ordinates of the target point and the positioning of the patient in the irradiation unit were in accordance with corresponding steps during an open stereotactic procedure.

**Hormone determinations**

Cortisol was measured in plasma using a fluorimetric method (de Moor et al. 1962; Laurell 1970, personal communication), cortisol in urine by radioimmunoassay (Ruder et al. 1972; Ficher et al. 1973), and TSH by radioimmunoassay using human TSH (Kabi) for standard and labelling. The antiserum (Kabi) was raised in rabbits against human TSH. The labelling was performed with the lactoperoxidase method. The separation of antibody-bound and free hormone was performed by the double antibody technique.

Immunoreactive prolactin, FSH and LH were determined by using available kits (Svensson et al. 1978). Somatomedin A in serum was determined by radioreceptor assay utilizing human placenta as matrix and somatomedin A for labelling (Hall et al. 1974, 1976). An arbitrary reference serum used as standard has been defined to contain one unit per ml.

The ACTH stimulation test with dexamethasone suppression was as follows: The subjects received 1 mg dexamethasone orally at 11 p.m. on the first day. Next morning at 8 a.m., 25 IU (1-24) ACTH tetracosactrin (Synacthen®, Giba) was given iv. Blood
samples for cortisol determination were drawn on the first day at 8 a.m., on the second at 8 a.m., and thereafter 1.5 and 2 h following the ACTH injection. In the TRH-test, 200 μg TRH (Thyrefact®, Hoechst) was given at 8 a.m. during fasting. TSH in plasma was measured before the injection and then after 20 and 60 min. The LH-RH-test was performed by measuring LH and FSH before and 20, 30, 60 and 120 min after 100 μg synthetic LH-RH (Hoechst).

RESULTS

The patients were observed from 14 to 20 months following treatment (Table 2).

Clinical findings

Within the first seven months after the irradiation there was a gradual improvement of the clinical symptoms in all 4 patients. The previously elevated blood pressure was normalized at 7 months in all 4 patients. In 3 of the patients
Table 2.
Results of treatment with pituitary gamma lesion in 4 patients with pituitary dependent Cushing's syndrome.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Dose (rad.)</th>
<th>Observation time (months)</th>
<th>Clinical Cushing's syndrome</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7000</td>
<td>20</td>
<td>complete remission</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>10 000</td>
<td>15</td>
<td>complete remission</td>
<td>ACTH insufficiency 7 months</td>
</tr>
<tr>
<td>C</td>
<td>10 000</td>
<td>14</td>
<td>complete remission</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>7500</td>
<td>14</td>
<td>improvement</td>
<td>0</td>
</tr>
</tbody>
</table>

there was a complete clinical remission. One of these patients (B) developed ACTH insufficiency. After 7 months he was admitted to hospital with a three weeks history of slightly elevated temperature, fatigue, headache, vertigo, and weight loss. He also complained of impotence after the treatment although distinct signs of hypogonadism were lacking.

The fourth patient (D) improved but after 14 months still had minor signs of Cushing's syndrome comprising slight changes of the body build and some muscular weakness. However, even in this patient the atrophy of the muscles and skin had improved considerably.

All patients were clinically euthyroid before as well as after treatment. Patients A and D had regular menstruations. In none of the patients was there any evidence of damage to the optic tract or any local or general complications of the irradiation.

Laboratory investigations

Cortisol. – The urinary excretion of cortisol decreased after irradiation in all 4 patients (Table 3). In patient A there was already normal cortisol excretion after 2 months, while in patient C there was a gradual decrease with normal values after 1 year. Subnormal values were found in patient B at 7 months when he had ACTH deficiency. Patient D showed improvement but had no complete remission, she had cortisol levels lower than prior to treatment but still above the normal range.
**Table 3.**

Cortisol in urine, nmol \( \cdot \) 24 h\(^{-1} \), prior to and following treatment for pituitary dependent Cushing’s syndrome with gamma lesion. Normal range for cortisol in urine is 83–276 nmol \( \cdot \) 24 h\(^{-1} \).

<table>
<thead>
<tr>
<th>Before treatment</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1035</td>
<td>1256</td>
<td>825</td>
<td>1842</td>
<td></td>
</tr>
<tr>
<td>3– 6 months</td>
<td>282</td>
<td>970</td>
<td>557</td>
<td>487</td>
</tr>
<tr>
<td>7– 9 months</td>
<td>43</td>
<td>505</td>
<td>484</td>
<td></td>
</tr>
<tr>
<td>10–12 months</td>
<td>97</td>
<td>*</td>
<td>267</td>
<td>444</td>
</tr>
<tr>
<td>13–15 months</td>
<td>146</td>
<td>*</td>
<td>173</td>
<td>380</td>
</tr>
</tbody>
</table>

* Cortisol replacement therapy.

**Fig. 2.**

Single dose dexamethasone test with ACTH stimulation. Test procedure: Day 1 at 8 a.m. plasma cortisol; 11 p.m. 1 mg dexamethasone per os. Day 2 at 8 a.m. plasma cortisol followed by 25 IU (1–24) ACTH i.v.; plasma cortisol at 9.30 and 10 a.m. – Broken lines indicate levels before treatment, solid lines levels after treatment. Figures indicate months after treatment. Shaded area = mean ± 2 sd for 112 controls without pituitary or adrenal disease.
Mean plasma cortisol levels decreased in all the patients following treatment. Patient D, with elevated cortisol excretion, showed a mean diurnal plasma cortisol level between 276 and 420 nmol/l. Temporally subnormal levels were found in patient A, but they returned to normal 15 months following treatment. Subnormal levels were found in patient B before substitution therapy with cortisone was started. No patient obtained a normal diurnal rhythm of cortisol although patient A had a tendency towards normal nyctohemeral variations.

The plasma cortisol levels after a single dose of dexamethasone were lower after than before treatment. The supranormal rise of plasma cortisol following ACTH administration decreased after treatment (Fig. 2).

Other pituitary functions. – The two female patients (A and D) who were within the fertile age had normal plasma levels of oestradiol, FSH, and LH at every examination. Patient C, who had passed the menopause, had elevated gonadotrophin and low oestradiol levels in the serum. The male patient (B) had subnormal plasma testosterone levels prior to treatment (5.6 nmol/l) but normal (18.1 nmol/l) after seven months (normal range 11–29 nmol/l). A normal rise of LH after LH-RH injection was found in all 4 patients, 3 to 4 months after therapy (Fig. 3).

Serum prolactin levels were in the normal range when analysed 3 to 4 months after therapy.

Somatomedin A levels in serum (normal range 0.74–1.67 U/ml) were all

![Fig. 3.](image_url)

Serum LH levels after administration of 100 µg of LH-RH in 4 patients with pituitary dependent Cushing's syndrome 3 to 4 months after pituitary gamma lesion.
Serum TSH levels after administration of 200 µg of TRH in 4 patients with pituitary dependent Cushing's syndrome 3 to 4 months after pituitary gamma lesion.

within the normal range of age-matched controls 3 to 4 months after treatment. This finding is inconsistent with growth hormone deficiency.

Serum T4 concentrations were within normal range at all examinations. The increase in TSH after TRH was normal in all patients 3 to 4 months following treatment (Fig. 4).

**DISCUSSION**

The present study demonstrates that clinical remission and lowering of the cortisol production in patients with Cushing's syndrome could be obtained with gamma lesion of the hypophysis. Three out of 4 patients were totally normalized, and the fourth showed partial remission with considerable reduction of cortisol excretion. The latter patient received a comparatively small dose, 7500 rad, and the irradiation has so far not been repeated.

The aim was to normalize cortisol secretion without causing pituitary insufficiency. One of our patients had to be given replacement therapy with cortisol since he presented symptoms and laboratory findings of ACTH insufficiency. It is at present not known whether this ACTH insufficiency will be permanent. There was no evidence of gonadotrophin or thyrotrophin insufficiency. The absence of complications and the effectiveness of the therapy have encouraged us to continue with this form of treatment.
Pituitary irradiation as treatment was first used successfully by Cushing himself in 1932 (Cushing 1982). In 1946, Luft (1946) reported favourable results in 6 out of 8 patients. In later series the selection of patients and doses given have varied considerably but, in general, treatment appears to have been favourable in approximately 50% of the patients (Heuschele & Lampe 1967; Ennuyer et al. 1969). When using strict biochemical criteria for cure – reestablishment of normal diurnal variations of plasma cortisol or a mean plasma cortisol concentration of less than 10 μg/ml – only 20% of the patients were cured (Orth & Liddle 1971).

With techniques allowing higher doses of radiation to be administered to the hypophysis the percentage of remission was higher. Pituitary radiation by high-energy charged alpha particles with total doses of 6000 to 15 000 rad, applied during 5 to 12 days, gave remission in approximately 60%; but approximately 20% of these patients needed replacement with cortisone (Lawrence et al. 1976). Similar results were obtained with pituitary implants of radioactive gold or yttrium. Thus, in patients with normal sella, Burke and co-workers reported complete remission in 65%. The results were poorer in patients with evidence of a pituitary tumour on X-ray (Burke et al. 1973). However, 55% of the patients required some form of replacement therapy afterwards.

Surgical hypophysectomy is used as an alternative to pituitary irradiation, and the introduction of microsurgical techniques has improved the previously poor results of this form of treatment. In a study of 20 patients, out of which 7 had been adrenalectomized before pituitary surgery, 14 (70%) were cured and 5 (36%) showed hypopituitarism (Hardy & Vezina 1976). These results are similar to the best results obtained with irradiation.

It is not yet possible to assess whether our patients are permanently cured by the gamma lesion. Firstly, the observation time is too short. Secondly, and most important, the underlying pathology in pituitary dependent Cushing’s syndrome is not yet defined as being either primarily hypothalamic or pituitary in origin. If Cushing’s syndrome is caused by an altered influence on the hypophysis by releasing hormones from the hypothalamus, definitive cure might only be expected after complete hypophysectomy. If a pituitary adenoma were the primary cause of the disease a definitive and complete remission could be expected after destruction of that tumour – in our hands by irradiation.

Convincing evidence for the pituitary as the origin of the disease has been provided in some instances, viz. pituitary stalk resection can fail completely to affect the hyperadrenocorticism although producing insufficiency of other pituitary hormones (Liddle 1972), and surgical enucleation of a pituitary microadenoma can give biochemical remission (Lagerquist et al. 1974; Burke et al. 1977).

A common pathology, presumably a pituitary tumour, has been suggested for all stages of pituitary dependent Cushing’s syndrome (Cook et al. 1976). This
conclusion was based on the realization that the ACTH suppression by dexamethasone was qualitatively similar in the untreated disease as well as following bilateral adrenalectomy. The treated subjects included both those with and without Nelson's syndrome (Cook et al. 1976). Furthermore, a pituitary adenoma was a common histological finding in patients with untreated Cushing's syndrome although only a minority had radiological evidence of a tumour (Burke et al. 1973).

Findings of abnormal secretion and pathological response in stimulation tests of pituitary hormones have been interpreted as evidence for a hypothalamic involvement in Cushing's syndrome (Krieger & Glick 1972; Krieger et al. 1976; Krieger & Luria 1977). Some of these findings can also be explained by altered characteristics of the receptor in a pituitary tumour since a number of substances — such as LH-RH, noradrenaline and glucagon — induced a rise of cyclic AMP in tissue homogenate from an ACTH-producing adenoma (Matsukura et al. 1977).

Although the presence of a pituitary tumour does not exclude the hypothalamus as the origin of the disease, current evidence favours a pituitary aetiology in at least some of the patients with pituitary dependent Cushing's syndrome. In Cushing's syndrome of pituitary origin improvement of the neurosurgical and the radiological techniques would increase the percentage of complete remissions. This has been achieved by removal of microadenomas in the anterior pituitary (see above). Identical results can be achieved with the present method of stereotactic radiosurgery. This method does not involve open surgery and has the advantage of being safe and free of complications. Furthermore, it can be applied without hospitalization of the patient.

REFERENCES


16

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