Symptomatic hypothalamic hypopituitarism following radiotherapy

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Summary

A patient is described who developed symptomatic hypopituitarism within 18 months of radiotherapy for nasopharyngeal carcinoma. Detailed investigation indicated a lesion at hypothalamic level. The effect of radiation on hypothalamic-pituitary function is discussed.

Introduction

The availability of hypothalamic-releasing hormones together with reliable assays of pituitary hormones in plasma have provided the means of accurate assessment of hypothalamic-pituitary function. A case is described of clinical hypopituitarism following radiotherapy to the head and neck, in which the use of these pituitary function tests has demonstrated damage at the hypothalamic level.

Case Report

A 53-year-old postmenopausal woman presented in 1973 with cervical lymphadenopathy, the histology of which was interpreted as an unspecifiable form of malignant lymphoma. She received radiotherapy (3000 rad) to her neck, both axillae and mediastinum. In January 1976 she experienced headaches, diplopia and right-sided facial swelling. Bilateral VIth nerve palsies and sensory impairment over her right lower face were found. She subsequently developed dysphagia, dysarthria and ataxia with cranial nerve palsies of IX, X, XI and XII and bilateral extensor plantar responses. An EMI scan was normal. In September 1976, radiotherapy (3500 rad) was administered to the base of the skull and brain stem area and the neurological deficits improved. Following a further cervical lymph node biopsy in January 1977 the diagnosis was revised to carcinoma of the nasopharynx. Further irradiation was given to the cervical lymph nodes (2500 rad) and nasopharynx (600 rad). She remained weak and unwell with progressive loss of weight. When reinvestigated in November 1977, she was found to be pale and emaciated with normal pubic and axillary hair. The

BP was 100/80 mmHg; plasma sodium was 124 mmol/l and chloride 95 mmol/l; haemoglobin was 13.0 g/dl. The results of pituitary function tests are shown in Table 1. Thyroid antibodies were not detected. Urinary 17-hydroxy-corticosteroid (17-OHCS) excretion was 9 μ mol/24 hr (normal 20-50) rising to 91 μ mol/24 hr after 3 daily i.m. injections of 1 mg depot tetracosactrin. Skull X-rays and lateral tomograms of the pituitary fossa showed no evidence of enlargement or erosion of the sella, and visual fields were intact on perimetry.

Replacement therapy with thyroxine and prednisolone resulted in immediate clinical improvement. Her BP increased to 120/90 mmHg, and plasma electrolytes returned to normal. While previously she had been so weak that she had had difficulty sitting up in bed, within 2 days of starting treatment, she had recovered normal muscle power. Two months after starting replacement therapy, her weight had increased by 5 kg. There was no clinical evidence of persisting hypopituitarism but the serum prolactin level remained markedly elevated at 2240 mu./l, at which time the serum thyroxine concentration (on treatment) was normal.

Discussion

This patient showed unequivocal evidence of hypopituitarism following radiotherapy for nasopharyngeal carcinoma. The delayed pituitary response to stimulation by TRH (Hall *et al.*, 1972) and LH-RH (Vigersky *et al.*, 1977) and the raised serum prolactin concentration were consistent with a defect at hypothalamic level. The observed rise in urinary 17-OHCS after injections of depot tetracosactrin demonstrated that adrenal hypofunction was secondary to ACTH deficiency. An insulin hypoglycaemia test was not performed because of the patient's poor physical condition.

Pituitary metastases have been reported at post-mortem in 25% of cases with nasopharyngeal carcinoma (Teoh, 1957). This patient, however, had no clinical or radiological evidence of direct involvement of the pituitary fossa or hypothalamus by tumour. In patients with hypopituitarism following

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TABLE 1. Basal plasma hormone levels and the response to stimulation

Hormone	Basal	Normal range	Stimulant	Minutes post-stimulation							
				0	20	30	60	90	120	180	
Thyroxine	17 nmol/l	45 – 160	–								
Triiodothyronine	0.95 nmol/l	1.4 – 3.0	–								
Thyrotrophin	2.39 mu./l	0.7 – 5.7	TRH, 200 µg	2.39	5.1	–	10.1	–	–	–	
Prolactin	1710 mu./l	20 – 360	–								
LH	0.8 u./l	*33 – 150	LHRH, 10 µg	0.9	–	1.0	1.2	1.3	1.2	–	
FSH	2.1 u./l	*9.7 – 120	LHRH, 10 µg	1.9	–	2.2	3.0	3.8	4.7	–	
LH	1.0 u./l		LHRH, 100 µg	0.8	–	1.7	2.0	1.8	2.0	1.7	
FSH	2.0 u./l		LHRH, 100 µg	1.9	–	2.1	3.0	4.1	5.4	5.5	
Cortisol (11-OHCS)	08.00 hr 0.35										
	23.00 hr 0.25	0.3 – 0.7	–								
	µmol/l										

* Values for post-menopausal women.

radiotherapy to the head, radiation damage to the hypothalamus has been implicated as the mechanism of pituitary dysfunction because the hypothalamus is considered more radiosensitive than the pituitary gland (Larkins and Martin, 1973; Samaan *et al.*, 1975; Rosenthal and Goldfine, 1975). This radiosensitivity would explain the hypothalamic hypopituitarism in this case despite the inclusion of the pituitary gland in the field of radiation. Although hypothalamic-pituitary abnormalities have been demonstrated after radiation to the head and neck, very few symptomatic cases of hypopituitarism have been described (Larkins and Martin, 1973; Tan and Kunaratnam, 1966). Previous lack of sensitive hormonal tests of hypothalamic-pituitary function may explain why hypopituitarism has seldom been recognised as a complication of radiotherapy, particularly as the non-specific symptoms of hypopituitarism may be ascribed to the primary malignant disease itself.

Pituitary deficiency has usually been reported as developing several years after radiotherapy (Larkins and Martin, 1973; Samaan *et al.*, 1975). This patient developed hypopituitarism within one year of direct radiation to the nasopharynx, although the hypothalamic-pituitary area was probably irradiated 6 months earlier during treatment of presumed brain stem metastases. The time interval between the radiation and clinical hypopituitarism may therefore be much less than the suggested minimum of 5 years (Samaan *et al.*, 1975).

It seems likely that endocrine abnormalities are a more common complication of radiotherapy to the head and neck than has previously been appreciated (Samaan *et al.*, 1975; Rosenthal and Goldfine, 1976).

The single most useful screening investigation is probably a serum prolactin level (Samaan *et al.*, 1975), elevation of which in this context indicates hypothalamic damage. Measurement of serum prolactin concentrations is therefore advisable before and at regular intervals after radiation of the head, to identify this complication at an early stage. Appropriate replacement therapy, as in this case, may transform the patient's clinical condition.

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