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PITUITARY ADENOMA*†

PREOPERATIVE SYMPTOMATOLOGY IN A SERIES OF 260 PATIENTS

BY

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STUDY of the syndromes associated with pituitary adenoma began with the description of acromegaly by Marie (1886), and many reports of the symptomatology of the tumour have since appeared (Cushing, 1912; Cairns, 1935; Henderson, 1939; Jefferson, 1940; Bakay, 1950; Younghusband, Horrax, Hurxthal, Hare, and Poppen, 1952; Nurnberger and Korey, 1953; Mogensen, 1957; Ray and Patterson, 1962; Poppen, 1963). Recently a series of 260 patients with pituitary adenoma selected for combined surgery and radiotherapy because of failing vision has been studied. Both the effect of treatment on vision (Elkington and McKissock, 1967) and the subsequent endocrine function (Elkington, Buckell, Monamy, and Jenkins, 1967) have been described elsewhere. The present communication reports the pre-operative symptomatology in these patients and suggests how early diagnosis of pituitary adenoma, necessary if the best results are to be obtained from treatment, may be made on clinical grounds.

Material and Methods

The case records of 260 patients were examined. They had been operated on by one surgeon at either the National Hospital for Nervous Diseases, Queen Square, or Atkinson Morley's Hospital, Wimbledon, between 1938 and 1962. The nature of the tumour had been confirmed by histological examination in 246; in fourteen the clinical and operative findings alone were accepted as diagnostic. Failing vision was the sole indication for operation in almost every instance, and detailed records of both the visual acuity and the visual fields were available. The former was expressed by Snellen or Jaeger reading type, and the latter was shown in charts of visual field obtained by perimetry. Quantitation of visual function using the method described by Colby and Kearns (1962) was not attempted, a simple descriptive classification being used for the visual fields. Evidence of endocrine function was not consistently recorded, and investigation of endocrine function was infrequent.

Findings

Of the total of 260 patients, 145 were males and 115 females. The youngest patient was aged 14 years and the oldest 72 years at the time of operation. The greatest incidence of symptoms necessitating treatment occurred in the fifth decade in both sexes. Details of age, sex, and tumour type are given in Tables I and II (opposite).

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TABLE I
AGE AND SEX DISTRIBUTION

Age Group (yrs)	Under 19	20–29	30–39	40–49	50–59	60–69	Over 70	Total	
								No.	Per cent.
Male	4	14	33	46	32	13	3	145	56
Female	6	11	13	35	30	16	4	115	44
Total No. per cent.	10 (4%)	25 (10%)	46 (17%)	81 (31%)	62 (24%)	29 (11%)	7 (3%)	260	100

TABLE II
TUMOUR TYPE AND AGE DISTRIBUTION

Age Group (yrs)	Under 19	20–29	30–39	40–49	50–59	60–69	Over 70	Total	
								No.	Per cent.
Chromophobe	5	20	38	58	48	24	5	198	76
Eosinophil	3	5	2	5	2	1	—	18	7
Mixed	2	—	3	13	7	3	2	30	11
Uncertain	—	—	3	5	5	1	—	14	6
Total	10	25	46	81	62	29	7	260	100

Vision

Since impairment of vision was the principal indication for operation almost all patients suffered from this symptom. Reduction in size of the visual fields was more marked than reduction in visual acuity, the loss usually appearing first in one or both of the upper temporal quadrants. The frequency of different types of visual field defect is given in Table III.

TABLE III
FREQUENCY OF DIFFERENT TYPES OF VISUAL FIELD DEFECT

Field Defect		No.	Per cent.
Bilateral temporal, all varieties		184	70·7
Unilateral temporal	All varieties (other eye normal)	24	9·2
	Other eye blind	14	5·4
	Central scotoma in other eye	5	1·9
Unilateral central scotoma		1	0·4
Homonymous and isolated nasal		13	5·0
None		3	1·2
Not recorded		16	6·2
Total		260	100

The reduction in area of the visual fields was rarely recognized as such at first. Collisions with other people or with objects in the home, or traffic accidents as either driver or pedestrian, rather than complaints of failing vision, were the reasons for presentation in many

instances; in others the patient observed altered appreciation of colour in one or both temporal fields. Most patients evolved techniques for reading whereby the areas of impaired vision were avoided; thus the defect in vision was frequently not recognized by the patient until considerable encroachment on the visual fields had occurred. Further delay took place even after the recognition of impaired vision, for this was usually attributed to the need for spectacles and a trial of lenses ensued. On average an interval of several months and in many instances of several years elapsed between the onset of visual symptoms and the diagnosis of pituitary adenoma.

Diplopia was another symptom often incorrectly explained; 98 patients complained of double vision in some degree, although a demonstrable ocular palsy was present in only fourteen. In the remainder diplopia was the result of bitemporal field defects and the consequent difficulty in accurately registering the image in each eye.

Headache

Severe headache occurred as a pre-operative symptom in one-third of the patients, and slight headache in another third. In many the headache was confined to the region of the orbit and nose, was unilateral, and preceded operation by several months or years. In eleven patients, however, the onset of headache was sudden and severe, and was accompanied by abrupt deterioration of vision with impairment of consciousness, as a result of tumour infarction. A distinctive pattern of headache occurred in five patients, in whom the headache abated with the onset of visual symptoms, probably owing to the escape of the tumour from the confines of the sella. Papilloedema was observed in one patient only.

Epilepsy

This condition was a pre-operative symptom in six patients; four suffered from grand mal, one from temporal lobe epilepsy, and one from uncinate fits. In four of these patients the tumour was found to have involved the cerebral hemisphere. The cranial nerves most frequently involved, after the optic chiasma, were the third, fourth, and sixth nerves. The oculomotor and abducent nerves were each involved in six patients, and in three patients there was both internal and external ophthalmoplegia. The remaining cranial nerves were infrequently involved: the trigeminal nerve in three patients, causing loss of sensation in the area of the ophthalmic division, and the facial nerve in one.

Symptoms and Signs of Endocrine Disorder

Pituitary Function

Evidence of altered pituitary function did not influence the selection of patients for operation, but the resulting symptoms and signs assisted in the diagnosis of the cause of impaired vision. Acromegaly occurred in each of the eighteen patients with an eosinophil tumour, and in one with a mixed cell tumour. Clinical evidence of impaired pituitary function often occurred in patients with chromophobe adenoma, but since the records were not always explicit on this subject the frequency of hypopituitarism in association with this tumour cannot be determined with precision. Acromegaly was, however, observed in two patients with a chromophobe adenoma. With the exception of overgrowth in acromegaly, the first symptoms to appear were always those of impaired gonadal function, such as loss of libido, partial or total impotence, amenorrhoea, or infertility. Impotence

and loss of libido, though readily admitted by the patient, were usually the cause of spontaneous complaint by the spouse only. Menstruation continued up to the time of operation in only twelve (25 per cent.) of 49 females aged 45 or under, and only six of these patients reported normal menstruation. Infertility was recorded as a pre-operative symptom in nine patients, in one of whom it was the initial complaint. Amenorrhoea did not necessarily indicate infertility; one patient became pregnant for the third time after amenorrhoea of 7 years duration and bore a normal infant, though lactation failed. In another instance excessive mammary hypertrophy occurred during pregnancy and persisted subsequently, though without galactorrhoea.

Hypogonadism

Changes in the skin and in the growth and distribution of hair were also early consequences of gonadal failure. The most frequent abnormality was pallor of the skin, together with a fine dry texture. Abnormalities in the growth and distribution of hair affected both sexes but was naturally more evident in males. Scalp hair was retained or even reappeared, but elsewhere on the body hair was reduced in quantity, a gradual process which usually preceded other symptoms by many years, though in two patients the onset of hair loss was abrupt.

Adrenal and Thyroid Function

The symptoms resulting from deficient adrenal and thyroid function were less easy to identify. Lethargy and loss of energy were frequent complaints, though more often recalled by the patient than specified in the case records. The systolic blood pressure proved of little value for diagnostic purposes, being less than 110 mm. Hg in only nine patients, seven of whom already had signs of hypopituitarism. Increased sensitivity to low temperatures, with difficulty in keeping warm, was another complaint associated with evidence of pituitary insufficiency. Approximately one-half of the patients complained of impaired tolerance to cold before the operation; in two instances it was the presenting symptom. Pre-operative weight gain was rarely great and appeared usually to be associated with the onset of pituitary insufficiency; weight loss did not occur.

Eosinophil Adenomata

The behaviour of eosinophil adenomata resembled that of chromophobe adenomata in most respects. The indications for operation were identical and the relief of acromegalic symptoms was not a consideration in the decision to operate. The age and sex distribution differed slightly from that of the chromophobe adenoma, with a slight excess of females over males and a lower average age. Symptoms and signs of hypopituitarism were uncommon before operation, but headache occurred in a larger proportion of patients than in association with chromophobe adenoma, and was more severe. Pain in the hands, especially at night, occurred in half the acromegalic patients, and probably resulted from compression of the median nerve in the carpal tunnel. Diabetes mellitus developed pre-operatively in only one instance, as did hyperhidrosis. Skeletal overgrowth and alteration in facial appearance were accepted with remarkable equanimity and were responsible for few complaints. Women naturally suffered more in this respect than men, especially when an element of gigantism also existed; clothing, especially shoes, proved their greatest difficulty.

Pre-operative Investigation

Radiography of the skull showed enlargement of the sella in 226 (97 per cent.) of the 234 patients in whom the result of this investigation was recorded. Ventriculography provided confirmation of the diagnosis but did not often provide other information of value. Studies of endocrine function were usually omitted, since failing vision demanded prompt treatment and no surgical decision depended upon the result of endocrine investigation. Those studies that were recorded had been obtained by many different sources over a period of 25 years from selected patients, and accordingly were not analysed.

Discussion

The findings of the present study of patients with pituitary adenoma selected for treatment by operation resemble those of previous reports (Henderson, 1939; Bakay, 1950; Younghusband and others, 1952; Nurnberger and Korey, 1953; Mogensen, 1957; Poppen, 1963). These investigations agree in finding that the tumour is slightly more common in males than in females, and that the maximum incidence of symptoms requiring treatment is reached between the ages of 40 and 50 years, though with a wide scatter between the second and eighth decades. The preponderance of chromophobe adenoma noted in the present series (76 per cent.) resembles that observed by previous reviews. The frequency of acromegaly in the present series (8 per cent.) is also in agreement with that observed in most previous studies. The greater frequency of acromegaly noted by Cushing (1912) and Henderson (1939) resulted from the early recognition of acromegaly and from Cushing's special interest in the syndrome.

The high proportion of patients with visual symptoms (99 per cent.) is a consequence of the method of selection for treatment, and occurs in other series in which patients without visual symptoms are not treated surgically. The commonest defect is loss of vision in one or both temporal fields; this occurred in the present series in 86 per cent. of all patients, in 67 per cent. in the series of Henderson (1939) and Bakay (1950), and in 80 per cent. in those of Younghusband and others (1952) and Mogensen (1957). Other visual field defects, such as homonymous hemianopia, are infrequent by comparison, but are important for their association with large and extensive tumours. Unilateral central scotoma was recorded in one patient, a rare defect noted by Walsh (1947) and Meadows (1949) as rendering the diagnosis of pituitary adenoma especially difficult.

The extent to which visual impairment is tolerated by the patient is remarkable. The delay thus introduced between the first visual symptom and the establishment of the diagnosis has been noted on many occasions (Falconer, 1946; Younghusband and others, 1952; Lyle and Clover, 1961) but has not yet been eliminated. If this could be achieved, the results of treatment would be improved.

The occurrence of ocular palsies in association with pituitary adenoma has been described by Symonds (1962); their presence is likely to indicate a large tumour, possibly infarcted. The more frequent non-paretic type of diplopia, first reported by Beckmann and Kubie (1929) and more recently by Chamlin, Davidoff, and Feiring (1955), seems to be less well recognized. Epilepsy occurs under circumstances similar to cranial nerve lesions, and its frequency pre-operatively in the present series (2·3 per cent.) resembles the incidence of 1·7 per cent. reported by Poppen (1963).

Several studies have attempted to estimate the frequency of pituitary insufficiency before operation (Younghusband and others, 1952; Nurnberger and Korey, 1953; Mogensen, 1957). Being, like the present study, retrospective, these are likely to underestimate the incidence of pituitary insufficiency through the omission of evidence of slight endocrine disorder. It is generally agreed that hypogonadal symptoms and signs are the first to appear, often many years in advance of those of adrenal and thyroid deficiency, and that their incidence is comparable to that of impaired vision (Mogensen, 1957; Ross, 1961). In the present study three-quarters of the female patients aged 45 and under suffered from amenorrhoea at the time of operation, while almost 90 per cent. had observed menstrual irregularity. Subjective complaints in males had a similar incidence. In the light of findings such as these, Lyle and Clover (1961) have pointed out that earlier diagnosis of the cause of visual failure would be possible if more attention were paid to the endocrine function of all patients with failing vision.

Summary

The case records of 260 patients with pituitary adenoma selected for treatment by combined surgery and radiotherapy between 1938 and 1962 have been studied. Males composed 56 per cent. of the patients, and the maximum incidence of the tumour was between the ages of 40 and 49 years. The youngest patient was 14 and the oldest 72 years old.

Owing to the selection of patients for treatment almost all suffered from impairment of vision. Loss of vision in one or both temporal fields occurred in 88 per cent. of all patients, or 93 per cent. of those in whom the visual fields were recorded. In many instances a delay of months or years intervened between the first symptoms of failing vision and the diagnosis of pituitary adenoma. Though diplopia was frequent, demonstrable ocular palsy and other cranial nerve lesions were rare, except in patients with tumour infarction, in whom multiple neurological lesions occurred. Symptoms and signs of endocrine disorder were frequent though usually slight, evidence of impaired gonadal function appearing first.

The early recognition of temporal field defects and of pituitary insufficiency would enable the diagnosis of pituitary adenoma to be made more rapidly; this diagnosis should always be considered when no explanation for failing vision can be found in the eye itself.

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