though one patient conceived during the sixth month of treatment with bromocriptine, the other patient, who had received placebo, still failed to conceive after nine months' subsequent treatment with bromocriptine. In our experience the degree of hyperprolactinaemia shown by these patients, when associated with amenorrhoea, is associated with a highly favourable response to bromocriptine.⁹ Our results, and those of Moore *et al*,⁶ suggest that prolactin measurements, though of prime importance in amenorrhoea, have little therapeutic relevance in patients with normal ovulatory menstrual cycles. Sarris *et al*¹⁰ reached a similar conclusion.

Our patients who conceived were significantly younger and had a significantly shorter history of infertility than those who did not become pregnant. These observations, which reflect the well-known effects of age and duration of infertility on fecundity,¹¹ emphasise the importance of reporting the ages and full clinical details of patients in studies of infertility, since these factors may override any putative therapeutic procedures. Though we cannot be certain whether it was the patient's age or the duration of infertility that carried the graver prognosis, we found that subtracting the number of years of infertility eliminated the difference between the ages of those who did and those who did not conceive; this suggests that, in patients in the age range studied here, the duration of infertility carries a more serious prognosis than does age alone.

Finally, it was interesting to note the high incidence of side effects and their equal distribution in the two treatment groups. The incidence of side effects in drug trials tends to reflect the intensity with which patients are warned of them and with which they are sought, and our results do not rule out specific side effects of bromocriptine treatment. Their equal distribution does, however, suggest that not only was allocation to treatment double-blind but also that the treatment remained double-blind throughout. We conclude that bromocriptine, in the dose and

duration used in this trial, is of no value in unexplained primary infertility.

We thank the supraregional assay service laboratory of the Institute of Nuclear Medicine of the Middlesex Hospital Medical School for the prolactin measurements, and Mr John Fox and the steroid unit of the department of chemical pathology at St Mary's Hospital Medical School for the steroid measurements. We thank Miss Diana Combe for statistical advice, Mr Jack Thirlwall for computer facilities, and Mrs Margo Goodwin for administrative help. Finally, it is a pleasure to acknowledge Dr Graham Kennedy, of Sandoz Products Limited, both for supplying bromocriptine and placebo and for financial help.

References

- Jacobs, H S, and Wright, C S, *British Journal of Hospital Medicine*, 1978, **20**, 652.
- Lenton, E A, Sobowale, O S, and Cooke, I D, *British Medical Journal*, 1977, **2**, 1179.
- Tietze, C, *International Journal of Fertility*, 1968, **13**, 385.
- Harrison, R F, in *Advances in Gynaecological Endocrinology, Proceedings of 6th Study Group of Royal College of Obstetricians and Gynaecologists*, ed H S Jacobs, p 205. London, Royal College of Obstetricians and Gynaecologists, 1979.
- Schulz, K D, *et al*, *American Journal of Obstetrics and Gynecology*, 1978, **132**, 561.
- Moore, D M, *et al*, *Lancet*, 1978, **2**, 1243.
- Franks, S, *et al*, *British Journal of Obstetrics and Gynaecology*, 1977, **84**, 241.
- Jacobs, H S, *et al*, *Clinical Endocrinology*, 1976, **5**, 439.
- Hull, M G R, Savage, P E, and Jacobs, H S, *British Medical Journal*. In press.
- Sarris, S, *et al*, *Clinical Endocrinology*, 1978, **9**, 543.
- Cooke, I D, in *The Natural History and Major Causes of Infertility, WHO Symposium on Advances in Fertility Regulation*, ed E Diczfalusy, p 88. Copenhagen, Scriptor, 1977.

(Accepted 2 March 1979)

Hypopituitarism in normal-pressure hydrocephalus

S G BARBER, N GARVAN

British Medical Journal, 1979, **1**, 1039-1041

Summary and conclusions

Hypothalamic hypopituitarism has been associated with the intermittent intracranial hypertension of "normal-pressure" hydrocephalus. Six patients with this condition were studied endocrinologically; five showed evidence of hypothalamohypophyseal insufficiency, and, though only one needed treatment, all needed continued assessment of their endocrine state during follow-up.

Thus hypothalamohypophyseal dysfunction is more common than might be expected. Tests of anterior pituitary function should be performed before surgical intervention, as such dysfunction may adversely affect survival and the response to ventricular shunting.

Introduction

Raised intracranial pressure has been assumed to be a cause of hypopituitarism since Simonds and Brandes described pituitary necrosis in a patient with a frontal glioma in 1926.¹ Many other reports of tumours and head injuries causing hypopituitarism followed.² The intermittent bursts of intracranial hypertension associated with normal-pressure hydrocephalus seemed instrumental in producing pituitary failure in one patient.³ We carried out this study to ascertain the incidence of endocrinological damage among such patients.

Patients and methods

Normal-pressure hydrocephalus was diagnosed in six patients on the basis of the history; clinical findings; pressure of cerebrospinal fluid (CSF); and results of a radioiodinated serum albumin scan, computerised axial tomography (CAT), and air studies. The patients (three men, three women) were aged 41-64 years (mean 55.2 years), and their histories were as follows.

Case 1—A 41-year-old man with a history of seven years' progressive mental deterioration, four years' gait disturbance, and six months' urinary incontinence. A CAT scan showed dilatation of the ventricular system with no increase in the subarachnoid space over the cortex, and air ventriculography showed that air could not be manoeuvred above the tentorium. Monitoring of the intraventricular pressure showed normal pressure over most of the 24 hours with rises exceeding 300 mm

Department of Medicine, General Hospital, Birmingham B4 6NH
S G BARBER, MB, MRCP, senior registrar

Department of Neurosurgery, Midland Centre for Neurology and Neurosurgery, Smethwick

N GARVAN, FRCSI, senior registrar

CSF during the night. Insertion of a low-pressure shunt system was followed by an excellent recovery.

Case 2—A 62-year-old man with five years' progressive mental deterioration and four years' loss of mobility and ataxia of gait. CAT scanning showed ventricular enlargement with no increase in the subarachnoid space over the cortex. On lumbar puncture the CSF pressure was normal. Insertion of a low-pressure Spitz-Holter shunt resulted in only slight mental improvement.

Case 3—A 62-year-old man, who had had some memory impairment for two years. He had received well-controlled anticoagulant treatment after a mitral valve replacement three years previously. He presented with two weeks' urinary incontinence and two months' frontal headaches and ataxia. On examination he was confused and disorientated with mild expressive dysphasia and spasticity of the lower limbs without weakness. He was ataxic and needed help with walking. His blood pressure was normal. The CSF pressure, CAT scan, and changes seen on air ventriculography were similar to those in case 1. There was no evidence of cerebral infarction. Insertion of a shunt system resulted in some improvement in gait and memory.

Case 4—A 43-year-old woman with a six-week history of progressive mental and physical slowing. She had no history of intracranial infection or haemorrhage. On examination she was almost mute. There was no evidence of weakness but generalised hyperreflexia and bilateral Babinski responses were apparent. Air cephalography showed communicating hydrocephalus with normal cortical sulci. Radioiodinated serum albumin scanning showed that most of the isotope was still within the ventricles at 52 hours. Shunting resulted in remarkable improvement within 24 hours, and her condition returned to normal.

Case 5—A 61-year-old woman, who first presented with a coma-producing subarachnoid haemorrhage. On admission she was conscious but confused and dysphasic. Bilateral carotid angiography carried out later showed no cause for the haemorrhage. Vertebral angiography was not performed. In the eight weeks after discharge to another hospital she developed progressive confusion and bilateral extensor plantar responses. Repeat carotid angiography was unhelpful. Air ventriculography showed ventricular dilatation with no air going above the prepontine level in the subarachnoid space. CSF pressure at lumbar puncture was normal. After shunting her condition returned to normal.

Case 6—A 61-year-old woman, who had had a right middle cerebral arterial aneurysm clipped three years previously. She presented again with pronounced dementia, ataxic gait, and incontinence, which had developed over 12 months. Monitoring of the intraventricular pressure showed appreciable rises at night. Air ventriculography showed communicating hydrocephalus with no air over the cortex. CSF shunting resulted in early improvement.

Endocrinological assessment included tests of basal thyroid function (thyroxine and triiodothyronine uptake) and measurement of basal androgen or oestradiol concentrations and the anterior pituitary responsiveness to thyrotrophin-releasing hormone (TRH), gonadotrophin-releasing hormone (GRH) and insulin-induced hypoglycaemia. All hormone assays were performed using methods detailed elsewhere⁴ and were subject to the national quality control criteria of the Supra-regional Assay Service. The reference standards for assays of thyroid-stimulating hormone (TSH), luteinising hormone (LH), follicle-stimulating hormone, prolactin, and growth hormone were MRC

68/38, 69/104, 69/104, 71/222, and 66/217 respectively. Since there were no suggestive symptoms, posterior pituitary function was not assessed.

Results

The table shows the results of the endocrinological tests. Results of tests of basal thyroid function were normal in all patients. Total androgen concentrations in all three men were low. The man in case 1 also had an abnormal response of LH to a bolus intravenous injection of GRH. LH responsiveness and androgen concentrations were restored by a two-week course of subcutaneous GRH, which disappeared after completion of the course.³ The low total androgen concentrations in the other men were associated with unexpectedly low basal LH concentrations. Oestradiol concentrations in the three women were compatible with their postmenopausal state, and all failed to show the expected rise in basal gonadotrophin concentrations or response to GRH. The response of TSH to TRH in the patient in case 6 was also absent. In cases 1 and 5 the TSH response to TRH was prolonged, which may suggest hypothalamic damage. Only one patient (case 1) had no growth-hormone response to insulin-induced hypoglycaemia and he also had a poor cortisol response to the same stimulus. The prolactin concentration was abnormally high in the patient in case 6, who was receiving thioridazine, prochlorperazine, and chlormethiazole. Pituitary tumours were not detected in any of the patients by conventional radiography.

Discussion

Pituitary failure is a recognised complication of head injuries and brain tumours. It occasionally results from other cerebral disorders such as intracerebral haemorrhages and infarcts² whose common aetiological factor may be oedema and raised intracranial pressure. The finding by Nakejima *et al*⁵ that in animals rises in intracranial pressure induced artificially using balloons can cause pituitary infarction supports this contention.

Normal-pressure hydrocephalus has only recently been shown to be associated with abnormal CSF pressures, though this was suggested in early descriptions of the syndrome. Although variations in CSF pressure occur during normal sleep, they are more pronounced in normal-pressure hydrocephalus, and efforts at treatment have concentrated on circumventing these pressure peaks. Despite earlier reports, the clinical response to shunting cannot be correlated with the severity of the abnormal pressure recordings nor with the incidence or severity of either dementia or gait disturbance.⁶ We believe that some patients may develop hypothalamohypophyseal impairment as a result of the severity and duration of these pressure anomalies, which will adversely affect patient response and survival.

Jacobs⁷ reported abnormal reactions to glucose tolerance tests in 17 out of 33 patients, but none appears to have had overt diabetes mellitus and this does not, therefore, appear to be an

Anterior pituitary function in six patients with normal-pressure hydrocephalus. (Times are minutes after test injection of 100 µg thyrotrophin-releasing hormone and 200 µg of gonadotrophin-releasing hormone and insulin)

Case No	Sex	Age (years)	TSH (mU/l)			LH (U/l)			FSH (U/l)	Cortisol (nmol/l)				Growth hormone (mU/l)					Pro-lactin (mU/l)	Total androgen (nmol/l)	Oestri-adiol (pmol/l)	Minimum glucose (mmol/l)
			0 min	30 min	60 min	0 min	30 min	60 min		0 min	60 min	90 min	120 min	0 min	30 min	60 min	90 min	120 min				
1	M	41	6	17	21	1	3	4	1	220	396	315	286	<1	2	3	2	1	444	1.1 7.1 10.0		1.9
2	M	62	2	7	5	4	29	29	16	509	751	877	804	<1	30	21	12	6	470			1.8
3	M	52	2	8	4	3	13	16	4	520	830	740		4	3	36	20		372			2.0
4	F	51	10	19	16	59	>120	>120	>50	740	890	1040	1150	1	4	69	135	123	260		50	0.6
5	F	61	7	10	12	7	39	39	45	390	790	710		2	5	15	17		480		<40	1.1
6	F	64	1	3	3	<1	1	1	2	600	820	950	630	1	2	28	39	11	2470		125	1.7
Normal ranges:			1-7	5-21	Less than 30-min sample	1-9* 12-49†	9-38* 21-117†	7-44* 43-113†	1-7* 45-71†	140-700 at 0 min, then an increment of 190 nmol/l				>15 at any time					<600	>14	>40	>2.2

*Men.

†Based on 10 postmenopausal women.⁸

TSH = Thyroid-stimulating hormone. LH = Luteinising hormone. FSH = Follicle-stimulating hormone.

Conversion: SI to traditional units—Cortisol: 1 nmol/l ≈ 0.036 µg/100 ml. Total androgens: 1 nmol/l ≈ 28.6 ng/100 ml. Oestradiol: 1 pmol/l ≈ 0.27 pg/ml. Glucose: 1 mmol/l ≈ 18 mg/100 ml.

important factor in the response to shunting. The mechanism of this carbohydrate intolerance may well be similar to that in our patients, whose endocrinological damage may have been primarily hypothalamic. The clinical importance of any pituitary insufficiency depends on its extent and permanence. In case 1 the defect appeared to be static and required long-term replacement treatment. Failure to provide such hormonal treatment might have rendered the dementia permanent simply by substituting a metabolic cause for a mechanical one. Weakness from the adrenocortical and androgen deficiencies may prevent an appreciable improvement in gait.

Thus five of our patients with normal-pressure hydrocephalus showed endocrine disturbance, which may affect immediate operative survival and the long-term response to treatment. We believe, therefore, that all such patients should be assessed endocrinologically before surgical intervention and, when necessary, replacement treatment started.

We wish to thank Professor W Butt, department of clinical endocrinology, Women's Hospital, Birmingham, for help with the assays, and Hoechst Pharmaceuticals Ltd, who supplied the gonadotrophin-releasing hormone.

References

- 1 Simonds, J P, and Brandes, W W, *Archives of Pathology*, 1926, **2**, 18.
- 2 Kovacs, K, *Neuroendocrinology*, 1969, **4**, 170.
- 3 Barber, S G, and Garvan, N, *British Medical Journal*, 1978, **1**, 817.
- 4 Kandeel, F R, et al, *Clinical Endocrinology*, 1978, **9**, 429.
- 5 Nakajima, T, et al, *Proceedings of Annual Meeting of the Japanese Endocrinological Society*, 1971, p 2.
- 6 *Lancet*, 1977, **2**, 1011.
- 7 Jacobs, L, *Journal of Neurology, Neurosurgery and Psychiatry*, 1977, **40**, 331.
- 8 Shaw, R W, MD thesis, Birmingham University, 1975.

(Accepted 1 March 1979)

Asthma in the elderly: an epidemiological survey

M L BURR, T J CHARLES, K ROY, A SEATON

British Medical Journal, 1979, **1**, 1041-1044

Summary and conclusions

A random sample of one in eight people aged 70 and over living at home in a south Wales town was surveyed to establish the prevalence of asthma. Subjects attended a screening clinic, where spirometry before and after an inhalation of salbutamol, skin prick testing, blood count, and sputum examination were carried out and a questionnaire answered. Those in whom asthma seemed at all likely were subsequently examined in detail in a chest clinic. Out of 485 subjects eligible, 418 (86.2%) were screened. Twelve (2.9%) had current asthma, of whom three had not previously been diagnosed as asthmatic and four were being treated but were unaware of the diagnosis. A further 15 (3.6%) had mild asthma or a history of the disease, giving a total prevalence of any history of asthma of 6.5%. Only one of the subjects who did not attend the screening clinic was known to have asthma, suggesting that the overall prevalence did not differ greatly from this figure. It was found that the disease might start or remit at any age.

Thus in the elderly current asthma is more prevalent in men than women (5.1% compared to 1.8%) and in terms of spirometry is more severe. Two underlying disease processes may perhaps exist that fulfil criteria for asthma in the elderly, one causing sputum eosinophilia and the other a form of chronic bronchitis with reversible airways obstruction.

Introduction

Asthma is difficult to diagnose in the elderly because it is often "intrinsic"—that is, it lacks those allergic characteristics that help to distinguish it in younger people—and because chronic bronchitis, which may cause similar symptoms, is common in old people. When partially reversible airways obstruction is present it is particularly difficult to distinguish between the two diseases. Because we had gained the clinical impression that asthma is common in the elderly and often undiagnosed we carried out a survey to discover the prevalence of asthma and reversible airways obstruction among old people living at home.

Subjects and methods

The survey took place in a south Wales town. We drew a random sample of one in eight of all people aged 70 years and over who were registered with the local general practitioners. Residents of old people's homes and long-stay hospital wards were excluded. The subjects were invited to attend a screening clinic or were visited at home. Those who reported a productive cough were given sputum pots containing 70% alcohol and asked to provide a specimen of sputum, which was examined for asthmatic stigmata.¹ At the clinic a short, detailed questionnaire was completed asking about respiratory symptoms. Wheezing was defined in terms of whistling,² and questions were asked about recent attacks ("Have you had an attack of shortness of breath with wheezing at any time in the last 12 months?"), nocturnal dyspnoea ("Has your sleep been disturbed by breathlessness or wheezing at any time in the last 12 months?"), and asthma ("Have you at any time in your life—even in childhood—had asthma?"). Lung-function tests, measuring forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC), were performed before and 15 minutes after inhalation of two puffs of salbutamol, using a vitalograph. Skin prick tests to house dust, mite extract (*Dermatophagoides pteronyssinus*), grass pollens, *Aspergillus fumigatus*, and cat fur were performed. Blood was taken for eosinophil counts and the subjects weighed and measured.

Subjects whose history and lung function suggested asthma were referred to a hospital chest clinic. These subjects comprised all those who claimed to have current asthma, who reported nocturnal dyspnoea, and who complained of wheezing and breathlessness during the previous 12 months and whose FEV₁ improved by 15% or more after an inhalation of salbutamol. At the chest clinic chest radiography was performed and the subjects were given a full clinical examination by a

MRC Epidemiology Unit, Cardiff CF2 3AS

M L BURR, MD, MFCM, epidemiologist

Llandough Hospital, Penarth, South Glamorgan

T J CHARLES, MB, MRCP, senior registrar (present appointment: consultant physician, Abergele Hospital, Abergele, North Wales)

K ROY, FIMLT, senior laboratory scientist

A SEATON, MD, FRCP, consultant physician (present appointment: director, Institute of Occupational Medicine, Edinburgh EH8 9SU)