Is “benign intracranial hypertension” really benign?

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SUMMARY Hypothalamic-hypophyseal insufficiency has been found in seven of eight patients with so-called benign intracranial hypertension, of whom four showed an inadequate adrenal response to stress. The syndrome of benign intracranial hypertension cannot therefore be considered entirely benign and patients should receive full endocrinological assessment and follow up.

The development of sensitive and specific tests of hypothalamic and pituitary function¹ has enabled the mechanisms of pituitary infarction to be re-examined. The ability to monitor intracranial pressures led to the detection of bursts of intracranial hypertension in “normal pressure” hydrocephalus² which have been implicated as the cause of hypothalamic hypophyseal damage in such patients.^{3,4} Since the intracranial pressure in patients with the syndrome of benign intracranial hypertension may be severe enough to cause blindness in addition to papilloedema,⁵ we decided to assess the endocrine status of such patients.

Patients, Materials and Methods

Nine patients aged 24–55 years (mean 41.9 years) were diagnosed as having benign intracranial hypertension on the basis of history, physical examination, and the absence of demonstrable pathology to explain the raised intracranial pressure. One patient was male and the others female. Anterior pituitary function was assessed in response to insulin-induced hypoglycaemia, thyrotrophin-releasing hormone (TRH), and gonadotrophin-releasing hormone (GnRH) after an overnight fast.¹ Basal samples were taken for routine blood count, biochemical profile, thyroxine, T3 uptake test, and either oestradiol or total androgen (depending on the sex of the

patient). All hormone assays were performed subject to the quality control criteria of the supraregional assay service, using methods described elsewhere.⁶ Blood sugar estimations were performed by the ferricyanide method of Technicon.⁷ All blood samples were taken via an indwelling forearm venous cannula. In the absence of suggestive symptoms, posterior pituitary function was not tested.

Results

Basal thyroid function (thyroxine and T3 uptake) tests were normal in all patients. The results of other endocrine tests are shown in the table. Only two patients (cases 2 and 6) had received steroids at any time and in the former they had not been given for six months before testing. The latter patient was on dexamethasone at the time of testing and this probably explains the blunted, sustained TSH response to TRH.

The cortisol response to insulin-induced hypoglycaemia was abnormal in five patients (cases 1, 4, 7, 8, and 9) and was not measured in the patient receiving dexamethasone. Although the basal resting cortisol levels were within normal limits, the response to stress was inadequate.⁸ All patients experienced definite symptoms of hypoglycaemia (see table). Growth hormone responses to the same hypoglycaemic stimulus were abnormal in five patients (cases 2, 4, 6, 7, and 8) although a rise from undetectable levels to 18 mU/l in case 6 probably represented “normal” function for a patient receiving steroids.

The luteinising hormone (LH) response to GnRH was abnormally sustained in three patients

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Table Results of anterior pituitary function testing

Case No	Sex	Age (yrs)	TSH (mU/l)			LH (U/l)			FSH (U/l)	Total androgen (nmol/l)	Oestra- diol (pmol/l)	Cortisol (nmol/l)			Growth hormone (mU/l)						Pro- lactin (mU/l)	Minimum blood sugar (mmol/l)		
			0	30	60	0	30	60				0	30	60	0	30	60	90	120					
1	F	26	8	33	26	2	22	24	2		Insufficient	710			610	560	470	15	29	41	30	22	250	1.9
2	F	47	11	18	15	28	64	80	50		40	470	2210		2210			1		4	3	2	220	1.8
3	M	55	7	15	10	2	18	14	10	29		650	880		880	960	740	12	16	49	56	34	360	1.8
4	F	49	7	11	10	58	113	113	50		45	560	480		640	540	460	37	7	9	2	4	240	1.8
5	F	42	7	20	15	1	28	25	3		410	450		940	910	790	2	24	29	46	28		850	1.8
6	F	24	10	13	13	1	9	6	2		100	50						1	1	18	5	1	164	2.6
7	F	53	9	15	14	27	74	82	50		40	540			650	570	490	18	3	1	1	1	220	2.0
8	F	44	24	64	24	86	44				55	510			640	510	370	1	1	2	2	2	200	1.0
9	F	37	11	33	26	2	7	5	3		280	440			510	530	450	1	2	24	42	10	460	1.9

Normal value:	1-7	5-21	30 min. sample	1-9†	9-38	7-44	1-7	> 14	> 40	140-700 then an increase of 190 over basal value	> 15 at any time	< 600	> 2.2
				1-26	7-80	3-75	1-26						
					12-21	43-49†		45-71					

Normal value: 1-7 5-21 30 min. sample 1-9* 9-38 7-44 1-7 > 14 140-700 then an increase of 190 over basal value > 15 at any time > 600 > 2.2

*Males.
†Females (at any stage of cycle).
‡Post-menopausal females.
Reference standards for TSH, LH, FSH, prolactin, and growth hormone assays were MRC 68/38, MRC 69/104, MRC 71/222, and MRC 66/217 respectively. 0', 30', 60', 90', and 120' represent time (minutes) after test injection of 100 µg TRH and 200 µg GnRH and insulin.

(cases 1, 2, and 4). In four patients (cases 2, 4, 7, and 8) the high basal levels of LH and FSH were compatible with their postmenopausal status. Basal prolactin levels were abnormal in one patient (case 5) with a rise to 3350, 3350, 2450, and 2950 mU/l at 30, 60, 90, and 120 minutes after TRH respectively. In the absence of a detectable pituitary tumour producing prolactin this also suggests hypothalamic damage.

Thus, of the eight patients not receiving corticosteroids at the time of testing, seven had abnormal pituitary responses to conventional testing and of these, four had an inadequate adrenocortical response to stress.

Discussion

Benign intracranial hypertension, pseudotumour cerebri, serous meningitis, and otitic hydrocephalus are names for a syndrome which is characterised by increased intracranial pressure for which intracranial mass lesions, obstruction of the cerebral ventricles, intracranial infection, hypertensive encephalopathy, and chronic carbon dioxide retention have been excluded and in which spontaneous recovery is usual. It may be associated with menstrual irregularity or amenorrhoea and has variously been reported as a complication of Addison's disease with improvement after replacement therapy⁹ and as being more likely to occur when steroid dosage is reduced and "relative adrenal insufficiency" is present.¹⁰ Our results show that hypothalamic-hypophyseal damage occurs in most patients with this condition. As early as 1926 Simonds *et al*¹¹ assumed that raised intracranial pressure caused pituitary infarction in their patient who had a frontal glioma. This presumption was supported by finding hypothalamic and pituitary damage in animals subjected to artificially induced rises in intracranial pressure using balloons¹² and in human patients after the transient bursts of intracranial hypertension found in so-called "normal pressure" hydrocephalus where all six patients tested had abnormal results.^{3,4} Therefore the endocrine disturbances in our patients were probably like the papilloedema and blindness, secondary to the rise in intracranial pressure. Such hypertension may cause herniation of the diaphragma sellae into the sella turcica¹³ with subsequent disturbance in pituitary function. Our patients showed no radiological evidence of the "empty sella syndrome" and the endocrine results suggest hypothalamic rather than pituitary damage. Moreover, the galactorrhoea which has occasionally been associated with benign intra-

cranial hypertension⁶ may be caused by hypothalamic damage leading to inadequate production of prolactin-release-inhibiting factor.

The difficulties in interpreting the results in patients receiving steroids are exemplified in case 6, where the TSH and growth hormone responses may have been due either to the steroids or to local damage, and the ACTH-adrenal response to stress could not be tested. In the light of the other results, patients such as these need reassessing after cautious withdrawal of steroids, and replacement therapy with steroids should be given for trauma or illness pending such reassessment.

So-called benign intracranial hypertension may not be completely benign and patients with this diagnosis should be assessed and followed up endocrinologically. Assessment should be performed after cessation of steroid therapy if this has been given, and if patients have an inadequate cortisol response to stress, replacement therapy should be started, as for other patients with adrenal insufficiency.

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