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MENINGISM AND PITUITARY COMA

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Non-iatrogenic hypopituitarism usually results from one of two pathological processes, post-partum pituitary necrosis (Sheehan & Summers, 1949) or pressure upon the secretory cells of the gland by tumour tissue. The former condition presents with features of adrenal, thyroid and gonadal hypofunction; the latter is manifest by a combination of these signs of hypopituitarism accompanied by visual failure due to chiasmal compression. Less commonly the first indication of pituitary failure is the clinical state described as pituitary coma. Disturbance of consciousness in hypopituitarism may be due to hypoglycaemia, hypotensive fainting attacks, acute adrenal crisis, myxoedema coma, and water intoxication. The

onset of impaired consciousness is commonly precipitated by operation (particularly those involving the skull), by infection, or the inadvertent administration of narcotics, insulin or intravenous fluids. These features are frequently superimposed upon those of chronic pituitary failure, that is dry skin, loss of axillary and pubic hair, vulval atrophy, pallor and puffiness of the face. However, these signs may be minimal in degree and therefore easily overlooked. Various reviews of the subject have been written by Sheehan and Summers (1949, 1952), Farquharson (1950), Allott and Simmons (1951), Ingraham, Matson and McLaurin (1952), Perkins and Rynearson (1952), Caughey and Garrod (1954), and Caughey (1958).

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We have recently observed a patient with hypopituitarism who presented with the clinical features of a meningitic illness. This unusual presentation is a potential source of diagnostic confusion and is thought to be worthy of recording in detail.

Case Report

A married woman aged 44 was admitted to hospital with a twelve-hour history of increasing tiredness and feeling cold. She retired to bed and was later found restless, confused and groaning. Her skin felt very hot. Examination in hospital at this stage revealed an ill-looking, extremely restless, semi-comatose woman with a temperature of 103° F. There was marked neck stiffness but no focal neurological signs were found.

A clinical diagnosis of meningitis was made but examination of the cerebro-spinal fluid did not substantiate this: (protein 60 mg., sugar 60 mg/100ml., cells: 5 lymphocytes/cu. mm.). The patient was given antibiotics and intragastric glucose fluids. During the following twenty-four hours no obvious improvement occurred and she was transferred to the Regional Neurological Centre. On arrival the patient was found to have temperature of 103° F., marked cerebral irritation, mild dehydration and marked neck stiffness. The blood pressure was 90/60 mm. Hg. and scattered rales were heard at both lung bases. She was pale with fine, dry skin, and over both shins were a number of tissue-paper scars. Pubic and axillary hair was absent and the vulva was atrophic. The optic fundi showed no abnormality. In the upper limbs the tone was increased and the tendon reflexes were brisk. In the lower limbs the deep tendon reflexes were unobtainable: both plantar responses were flexor.

At this stage the skull and chest X-rays were found to be normal. Examination of the peripheral blood showed: Hb, 15g./100 ml. w.b.c., 13,000/per cu. mm.: ESR 54 mm./hr. Lumbar puncture: CSF pressure normal, protein 42 mg/100 ml.: cells, 6 lymphocytes/cu. mm. The EEG showed a generally slow record with a gross excess of slow rhythmical delta activity in both frontal regions, suggesting a

projected discharge from some primary disturbance in the midline structures. The patient was given antibiotics and rectal saline infusion.

A few hours after admission a more detailed history became available from the husband. Sixteen years before (at the age of 28 years) at the birth of her fifth child, she had a retained placenta and a severe postpartum hæmorrhage. She had been delivered at home and needed resuscitation and transfusion by the local flying squad. She was apparently unconscious for a few hours. Several days later she developed ulcers on both shins. She failed to lactate, had persisting amenorrhœa, and remained very pale and lethargic. She lost weight, the axillary and pubic hair fell out and the patient became intolerant of the cold. In recent years the patient has had attacks of anorexia, extreme lethargy and confusion lasting two to three days. These episodes have usually been precipitated by a trivial upper respiratory tract infection. Investigations carried out in 1952, (routine flying squad follow-up) showed the patient to be clinically and biochemically hypopituitary. BMR minus 13 per cent; the 24 hr. urinary 17KS excretion 1.5 mg.: a glucose tolerance curve showed a fasting blood sugar of 20 mg./100 ml. followed by values of 53, 50, 50, 45, 45, at half-hour intervals after 50 g. of glucose. The patient at this time refused further follow-up appointments and treatment was never instituted.

On obtaining this history a provisional diagnosis of hypopituitary coma was made, but specific therapy was withheld because the patient appeared to be making a spontaneous recovery. On the following morning (12 hours after admission) the patient had so improved that neck stiffness was no longer evident, she was afebrile and quite rational. She confirmed the history outlined above.

Investigations. Skull and chest radiographs were normal, and culture and microscopy of urine and stools were negative. Serum electrolytes: Na. 139: K. 3.4; Cl. 95; Carbon dioxide 20 mEq/l. Blood urea, 61 mg./100 ml. Blood sugar, after 48 hours fast (after recovery) 39 mg./100 ml., in the absence of hypoglycæmic symptoms. Glucose tolerance test after 50 g. oral glucose, 60, 127, 79, 73, 106, 84 mg/100 ml. at 30 minute intervals.

TABLE I TESTS OF THYROID FUNCTION

B.M.R.	...	...	...	...	...	...	...	...	...	—13 per cent
Serum Cholesterol	...	...	...	...	...	...	...	...	...	268 mg./100 ml.
Serum P.B.I.	...	...	...	...	...	...	...	...	...	4.1 g./100 ml.
24 Hour Neck Uptake of ¹³¹ I	...	...	...	...	...	...	...	...	...	27 per cent of dose
ECG	R1 11 mm.	R2 7 mm.	R3 0 mm.	R4 7 mm.	T1 1 mm.	T2 1 mm.	T3 0 mm.	T4 1 mm.		

TABLE II TESTS OF PITUITARY ADRENAL FUNCTION

Basal Plasma Cortisol					2.0 µg. per 100 ml.
Basal 24 hour urine	17 KS	0.85	0.88	2.07 mg./	
	17 OHCS	4.0	3.0	2.3	24 hours
ACTH 3 × 80 units	17 KS	1.7	1.6	2.7 mg./	
	17 OHCS	4.1	1.2	0.7	24 hours
Methoppyrapone 3 g. daily	17 KS	0.4	0.5	mg./	
	17 OHCS	7.8	3.0	24 hours	

The results of specific biochemical investigations are shown in Table 1 and 2.

Urinary 17KS were estimated by the method of the M.R.C. Committee on Clinical Endocrinology (1951) and urinary 17-hydroxycorticosteroids by the method of Appleby, Gibson, Norymberski and Stubbs, (1955). A standard ACTH test (Renold, Jenkins, Forsham and Thorn, 1954) was performed, measuring urinary steroids on the third, fourth and fifth day after commencement of an intravenous infusion of ACTH, 80 units on each of three consecutive days. An increase of 50 per cent in urinary corticoids is necessary to demonstrate a normal response (Thompson & King 1959). The electrocardiographic changes in hypothyroidism and hypoadrenalism consist of reduction of amplitude of the T waves in standard leads (usually less than 6 mm. in leads 1+2+3); a diminished voltage of the QRS complexes in standard leads and in the anterior chest leads (R1+2+3 less than 25 mm.).

The metyrapone (Methopyrapone, SU4885) test was performed by the method of Marks (1962) giving 3 g. in divided doses by mouth daily for four days, and assaying urinary steroids on days four and five, this time being optimal for detecting the maximum rise. A metyrapone response of less than 10 mg./day (total 17 OHCS), or a rise of less than twice the basal levels, indicates a specific impairment of pituitary adrenal function, (Liddle, Island and Meador 1962; Marks and Summers, 1963).

Discussion

This lack of an adrenal response to intravenous ACTH, and the negative metyrapone tests indicated that the adrenal glands were incapable of a response to ACTH. This is probably a reflection of the long-standing atrophy of these glands consequent upon hypopituitarism of nearly sixteen years duration. Primary hypoadrenalism is excluded in this case by the absence of pigmentation taken together with the normal values of electrolytes on admission—at a stage when the patient was in coma. The tests of thyroid function were at the lower limit of normal in this patient, indicating that there was a relatively disproportionate degree of adrenal and gonadal hypofunction compared with thyroid function. Similar cases have been described by Sheehan (1961). These findings in conjunction with the striking clinical features of secondary hypogonadism leave no doubt that this patient suffers from hypopituitarism.

The history clearly points to a postpartum necrosis of the gland as the underlying cause. The detailed clinicopathological findings and variants of postpartum necrosis of the pituitary have been described by Sheehan and his colleagues (Sheehan and Summers, 1949, 1952, Sheehan, 1954, 1958, 1961, Sheehan and Stanfield, 1961, and Sheehan and Whitehead, 1963), and the clinical signs in this patient closely correspond to these descriptions. Of the tests available for the assessment of the integrity of the pituitary-adrenal axis, the metyrapone test is generally agreed to be the most sensitive in the detection of minimal dys-

function (Brownie and Sprunt, 1962; Marks and Summers, 1963). The negative metyrapone response in the present patient is indicative of impairment of pituitary-adrenal function and the failure of the adrenal response to endogenous ACTH was paralleled by a similar negative response to exogenous ACTH. The pathology of these cases has until recently been ill-defined, but it is of interest that Sheehan and Whitehead (1963) have recently demonstrated that in cases of postpartum pituitary necrosis who died within 35 days of 'delivery', a clear relationship exists between the severity of the necrosis of the anterior lobe and the occurrence of vascular lesions in the neurohypophysis. It is postulated that prolonged vascular spasm produces damage to vessels in the stalk, and that the subsequent re-establishment of a blood flow produces thrombosis in these vessels, which, if extensive, might lead to damage to the posterior lobe on rare occasions. By contrast in the late cases, examined many years after postpartum necrosis of the anterior lobe has occurred, the neural stalk shows no recognisable lesions, but atrophy or scarring are seen frequently in the posterior lobe. Sheehan and Whitehead believe that there is no evidence that the acute lesions seen occasionally in the posterior lobe lead to the more commonly found lesions in late cases.

A meningitic picture as the presenting feature of hypopituitary coma has been reported in the literature (Sheehan, 1958; Wilson, 1953; Caughey and Garrod, 1954). The most detailed account is that of Blau and Hinton (1960), but even this account lacks full biochemical confirmation of the pituitary hypofunction. Sheehan (1958) has divided cases of hypopituitary coma into two distinct groups: a spastic type, and a flaccid type. In the former, the arms and legs are rigid and flexed in the foetal position, the neck is stiff and the reflexes may be brisk, with a Babinski response. Muscular twitching is seen in the face and arms on occasions. The flaccid type is characterised by diminished or absent tendon reflexes, dilated pupils, and double incontinence. The patient described in this paper most closely resembles the spastic type, yet the absent reflexes in the legs, and flexor plantar responses clearly indicate that some overlap occurs between these two groups, and the distinction is probably an artificial one.

Cases of the type described above could easily be confused with pituitary apoplexy, in which signs of meningeal irritation may be prominent and so mimic a ruptured aneurysm (Brain, 1962). Other conditions to be considered in the differential diagnosis are subarachnoid haemorrhage, in which the onset is usually more abrupt and headache more severe, cerebral infarction in which focal signs are more prominent and cerebral abscess in which the onset is insidious and in which apathy is more usual than coma, and focal signs and a source of infection are commonly

apparent. Encephalitis may produce similar meningitic signs and impaired consciousness; however, the onset is usually more gradual and a pleocytosis is found in the cerebro-spinal fluid. We can offer no satisfactory explanation for the signs of meningism, and the mechanism remains obscure.

It is often difficult to determine the precipitating factor in hypopituitary coma. In the present case it is suggested that an upper respiratory infection was the provocative factor in the absence of other commonly implicated precipitants.

The patient responded to empirical therapy without specific replacement of corticosteroids or thyroid analogues. The electroencephalogram recorded after the initial stage of coma showed persistent theta activity at five to seven cycles per second with a peak amplitude of 100 microvolts and delta activity at three to four cycles per second of similar amplitude, predominant in

the anterior regions. These changes did not disappear on visual attention and are similar to those reported by Hughes and Summers (1956) in hypopituitarism. Specific replacement therapy has been reported to produce improvement in the EEG appearance according to Boselli and Jefferson (1957). These EEG changes, though typical, are not specific and therefore are not of diagnostic value.

In obscure cases of coma with meningitic signs, hypopituitarism must be considered in the diagnosis especially since specific replacement therapy may be life-saving.

Summary

A patient with Sheehan's syndrome is described, who presented with an illness characterised by both coma and severe meningism. The diagnostic problem posed by such cases is discussed, and the investigations and literature are reviewed.

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