Endocrine function in multiple sclerosis

P. MILLAC, D. B. COOK, AND KENNETH CHASE

From the Departments of Neurology and Clinical Biochemistry, Royal Victoria Infirmary, Newcastle upon Tyne

It is recognized that exacerbations of multiple sclerosis (MS) may be related to a variety of stressful situations more frequently than could be accounted for by coincidence (*British Medical Journal*, 1967). There is evidence that ACTH therapy benefits acute relapses of the disease and in recent years an intriguing relationship between demyelination and adrenal disease has been recognized (Eadie, 1966). Such considerations have instigated many investigations into endocrine function of MS patients. Only relatively recently, however, have techniques been sufficiently refined to permit more than a fairly crude estimate of a patient's endocrine status. Observations by Garcia-Reyes, Jenkins, Forsham, and Thorn (1952) and Alexander, Cass, Enders, and Sarai (1966) suggested that adrenocortical function is normal in multiple sclerosis. In a preliminary investigation Teasdale, Smith, Wilkinson, Latner, and Miller (1967) also concluded that adrenocortical responses were normal in multiple sclerosis but found that the rise in plasma cortisol seen with insulin-induced hypoglycaemia was significantly less than that of healthy controls. On the basis of these findings they indicated the possibility of an impaired stress response, mediated at the hypothalamic level, in multiple sclerosis. The present investigation extends these observations by assessing the entire cerebro-pituitary-adrenocortical axis in a group of MS patients, making comparisons with other patients in the neurological ward and a group of healthy subjects.

SUBJECTS AND METHODS

Thirty patients with multiple sclerosis were studied. There were 12 males and 18 females. Sixteen patients had developed fresh symptoms and signs in the fortnight before admission and are referred to as the acute cases. In the remainder (chronic group) the disease had been clinically quiescent for at least a year. All patients were ambulant before hospitalization and none had pressure sores or intercurrent systemic disease. None had received steroid therapy in the year before admission or a prolonged course of such treatment at any time. For comparison, 20 patients of similar age, sex, and duration of

hospital stay, but with a variety of neurological diseases other than demyelinating disease, were investigated with their knowledge and consent. Of these patients, five had been investigated with negative results for a variety of symptoms of which headache was the most prominent. Definitive diagnoses were cerebral tumour (2), syringomyelia (3), prolapsed intervertebral disc (3), migraine (2), familial ataxia (1), chorea (1), neurofibromatosis (1), and radiation myelopathy (1). One young woman had multiple cranial nerve palsies for which no cause was apparent after one year's follow-up. In addition the response of 12 healthy subjects to lysine⁸-vasopressin (LVP) was measured. For all tests, subjects fasted overnight and remained at rest during the procedure. At least 24 hours elapsed between procedures, which commenced at 9.30 a.m. and were carried out in random sequence. Blood samples were collected by repeated venepunctures into heparinized tubes and plasma cortisols were determined using the method of Stewart, Albert-Recht, and Osman (1961) by one of us (D.B.C.) who was unaware of the source of individual blood samples.

Adrenocortical function was measured by the method of Wood, Frankland, James, and Landon (1965). Plasma cortisols were determined immediately before and 30 minutes after the intramuscular injections of 0.25 mg of a synthetic polypeptide, β 1-24ACTH (Synacthen, Ciba), dissolved in 1.0 ml. physiological saline. The plasma cortisol response to LVP was measured in the manner described by Gwinup (1965). Blood was drawn for plasma cortisol determinations immediately before and 30, 60, 90, and 120 minutes after an intramuscular injection of 10 pressor units of synthetic LVP (Sandoz, batch no. 67001).

Plasma cortisol responses to insulin induced hypoglycaemia were determined by the technique of Greenwood, Landon, and Stamp (1966). Cortisol estimations were made immediately before and 30, 60, 90 and 120 minutes after the intravenous administration of 0.15 units insulin per kg body weight.

RESULTS

No untoward reactions were encountered throughout this trial, and no patient required dextrose during induced hypoglycaemia.

RESPONSE TO SYNACTHEN There was no significant difference in the mean rise in plasma cortisol seen in acutely relapsed MS patients, chronic MS cases, or

neurological controls (Table I). Basal cortisol values were lower in the patients with chronic multiple sclerosis than the other two groups, but the means did not differ significantly.

RESPONSE TO HYPOGLYCAEMIA Fasting blood sugars did not differ significantly between the three patient groups (Fig. 1). The mean fall in blood sugar was also similar but blood sugars returned towards the basal level somewhat more slowly in the chronic MS patients. In all three groups there was a significant rise in plasma cortisol 60 minutes after injection of insulin (Fig. 2, Table II). A smaller increment was seen in acutely relapsed MS patients than in chronic MS cases ($P < 0.02$) but in neither of these groups did it differ significantly from that in patients with other neurological diseases. Basal plasma cortisol readings for the acute MS patients were higher than those for the neurological controls and the means differed significantly ($P < 0.05$). Plasma cortisol levels tended to fall back to their initial levels more slowly in both acute and chronic MS patients.

RESPONSE TO VASOPRESSIN It has been noted that subjects may fail to respond to LVP for no apparent reason (Wynn, 1967). In this series a non-reactor was arbitrarily defined as an individual showing a rise in plasma cortisol of less than 5 $\mu\text{g/ml}$. (Czarny, James, Landon, and Greenwood, 1968). There were two non-reactors among the 14 MS patients studied, none in the 14 chronic cases, four out of 20

neurological controls, and two among the 12 healthy subjects. All patients who did not respond to LVP showed good responses to insulin hypoglycaemia. Results from non-reactors were not included in the subsequent analysis.

The incremental responses to LVP were very similar in the four groups of subjects (Table III). However in both groups of patients with multiple sclerosis the response fell away more slowly, resulting in significantly higher plasma cortisol levels at 60 minutes (acute and chronic MS) and 90 minutes (acute MS) than in neurological control cases. The plasma cortisol levels in MS patients were significantly greater than those of healthy control subjects at each sampling time.

DISCUSSION

The endocrine responses of patients with multiple sclerosis did not differ greatly from those given by patients with other neurological disorders. During hypoglycaemic stress MS patients gave mean plasma cortisol values in close agreement with those obtained by Teasdale *et al.* (1967). These workers suggested that the response by their MS subjects was impaired, as the mean increment in plasma cortisol was significantly less than that encountered in a previous series of healthy controls. They therefore suggested that a degree of hypothalamic impairment may be present. Yet in this study there was no significant difference between the incremental responses of MS

TABLE I
PLASMA CORTISOL AFTER SYNACTHEN (0.25 mg) IN MULTIPLE SCLEROSIS PATIENTS AND THEIR CONTROLS

Subjects	No.	Males/females	Mean ($\pm$ SEM) plasma cortisol ($\mu\text{g}/100$ ml.) after Synacthen		
			0 min	30 min	Increment
Acute MS	13	4/9	14.0 $\pm$ 1.4	24.4 $\pm$ 1.6	10.4 $\pm$ 1.2
Chronic MS	12	4/8	11.1 $\pm$ 0.9	23.4 $\pm$ 1.7	12.3 $\pm$ 1.4
Neurological controls	17	9/8	14.1 $\pm$ 1.0	24.5 $\pm$ 1.1	10.3 $\pm$ 1.4

TABLE II
PLASMA CORTISOL AFTER INTRAVENOUS INSULIN (0.15 u./kg) IN MULTIPLE SCLEROSIS PATIENTS AND THEIR CONTROLS

Subjects	No.	Age (yr)	Males/ females	Mean ($\pm$ SEM) plasma hydrocortisone ($\mu\text{g}/100$ ml.) after insulin injection					
				0	30 min	60 min	90 min	120 min	Mean maximum increment
Acute MS	14	35.6 $\pm$ 3.1	5/9	16.5 $\pm$ 1.6 ($P < 0.05$)	15.1 $\pm$ 1.2	22.4 $\pm$ 1.0	21.4 $\pm$ 1.3	20.2 $\pm$ 1.4	7.2 $\pm$ 1.3
Chronic MS	12	43.3 $\pm$ 2.9	4/8	13.0 $\pm$ 1.1	13.2 $\pm$ 1.5	23.1 $\pm$ 1.4	23.2 $\pm$ 1.4	21.7 $\pm$ 1.7 ($P < 0.05$)	12.4 $\pm$ 1.6
Neurological controls	19	40.7 $\pm$ 3.3	9/10	12.7 $\pm$ 0.9	14.6 $\pm$ 0.9	21.9 $\pm$ 0.7	21.0 $\pm$ 1.0	17.9 $\pm$ 0.9	10.4 $\pm$ 1.2

P values shown where means differ from those of the neurological controls.

FIG. 1. Mean blood sugar response to insulin (0.15 u./kg).

FIG. 2. Mean plasma cortisol response to insulin (0.15 u./kg).

TABLE III

PLASMA CORTISOL AFTER INTRAMUSCULAR LYSINE VASOPRESSIN (10 UNITS) IN MULTIPLE SCLEROSIS PATIENTS AND THEIR CONTROLS

Subjects	No.	Mean age ($\pm$ SEM) (yr.)	Males/ females	Mean ($\pm$ SEM) plasma cortisol (μ g/100 ml.) after injection of LVP					
				0	30 min	60 min	90 min	120 min	Mean maximum increment
Acute MS	12	34.7 ($\pm$ 3.2)	5/7	15.3 ($\pm$ 1.04) ($P < 0.05$)	24.3 ($\pm$ 1.53)	24.4 ($\pm$ 1.5) ($P < 0.05$)	22.0 ($\pm$ 1.38) ($P < 0.0125$)	17.0 ($\pm$ 1.24)	11.0 ($\pm$ 0.89)
Chronic MS	14	41.3 ($\pm$ 3.2)	6/8	14.0 ($\pm$ 1.0)	22.5 ($\pm$ 1.4)	24.3 ($\pm$ 1.4) ($P < 0.025$)	20.6 ($\pm$ 1.3)	16.3 ($\pm$ 1.3)	10.9 ($\pm$ 1.6)
Neurological controls	16	41.5 ($\pm$ 3.2)	7/9	13.1 ($\pm$ 0.78)	22.1 ($\pm$ 0.66)	20.9 ($\pm$ 1.1)	17.7 ($\pm$ 1.11)	15.3 ($\pm$ 0.91)	10.0 ($\pm$ 0.62)
Healthy controls	10	31.1 ($\pm$ 6.3)	4/6	11.6 ($\pm$ 0.67)	19.7 ($\pm$ 0.87)	19.9 ($\pm$ 1.1)	17.1 ($\pm$ 1.3)	12.5 ($\pm$ 0.93)	10.0 ($\pm$ 0.91)

P values given where means differ from those of neurological controls.

Healthy controls differed significantly from both groups of MS patients at all sampling times.

patients and their hospitalized controls with other neurological disorders, though a difference was observed between acute and chronic cases. This may imply a generally impaired response to such stress in hospitalized patients, though this was not the experience of Greenwood *et al.* (1966).

In the same manner incremental responses in

plasma cortisol after injection of LVP were comparable in MS patients, both acute and chronic, neurological controls, and healthy subjects. Multiple sclerosis patients did differ from other groups by sustaining high plasma cortisol levels for longer. Thus mean plasma cortisols for acute MS patients were significantly raised above those of the neuro-

FIG. 3. Mean plasma cortisol response to LVP (10 u.).

logical controls at 60 and 90 minutes after injection of LVP (Table III, Fig. 3). A similar trend was evident in the group of chronic MS patients and it was also evident at the end of the insulin sensitivity test. We would hesitate to attach too much importance to the present evidence of increased corticotrophic activity in multiple sclerosis. The LVP test is generally regarded as a valid measure of pituitary function (Gwinup, Steinberg, King, and Vernikos-Danellis, 1967) but the precise site of action of LVP is still uncertain and the phenomenon of non-reactors unexplained. There is still a paucity of experience using LVP as a quantitative as opposed to qualitative test of pituitary responsiveness.

In agreement with observations made by others there was no detectable disorder of adrenocortical function in multiple sclerosis. Mean basal cortisol values of acute MS patients were significantly raised above those of neurological controls in both the insulin sensitivity and LVP tests. This probably reflects a non-specific stress reaction to acute illness (Cope, 1965). The high basal readings might be expected to influence peak values and emphasize the importance of noting incremental responses, as well as the highest plasma cortisol level attained.

Some diminution in endocrine activity or reserve might be anticipated in debilitated MS patients with extensive disease and periventricular demyelination. While subtle compensatory pituitary changes in the cerebro-adrenocortical axis have possibly been demonstrated in this sample of moderately disabled patients, the magnitude of the alterations in endocrine function presents no support for the contention that such mechanisms have a role in the evolution of the disease.

SUMMARY

Plasma cortisol responses to adrenocortical stimulation, insulin-induced hypoglycaemia, and lysine-vasopressin have been measured in a group of multiple sclerosis patients and compared with those of patients with other neurological diseases but of similar age, sex, and duration of hospital stay. Basal

cortisol values were increased in acutely relapsed MS patients, but an increase in plasma cortisol of similar extent was seen in response to insulin-induced hypoglycaemia in MS patients and neurological controls. Although there was a comparable increment in plasma cortisols after injection of lysine vasopressin in the MS group and their controls, the high cortisol levels were sustained for longer by the former.

We wish to thank Professor Henry Miller for permission to study patients in his care, and Professor A. L. Latner for his encouragement and guidance. P.M. and D.B.C. acknowledge with gratitude financial assistance from the Multiple Sclerosis Society of Great Britain. Kenneth Chase was supported by a Medical Scientist Fellowship from the Life Insurance Medical Research Fund.

REFERENCES

- Alexander, L., Cass, L. J., Enders, M., and Sarai, K. (1966). Adrenocortical response to high dosage ACTH therapy in patients with multiple sclerosis. *Confin. neurol. (Basel)*, **28**, 1-17.
- British Medical Journal* (1967). Editorial: Precipitant of multiple sclerosis. *Brit. med. J.*, **2**, 192-193.
- Cope, C. L. (1965). *Adrenal Steroids and Disease*, p. 51. Pitman, London.
- Czarny, D., James, V. H. T., Landon, J., and Greenwood, F. C. (1966). Corticosteroid and growth-hormone response to synthetic lysine vasopressin, natural vasopressin, saline solution and venepuncture. *Lancet*, **2**, 126-129.
- Eadie, M. J. (1966). The association between diffuse sclerosis and Addison's disease. *Proc. Aust. Ass. Neurol.*, **4**, 63-67.
- Garcia-Reyes, J. A., Jenkins, D., Forsham, P. H., and Thorn, G. (1952). Adrenocortical function in multiple sclerosis. *Arch. Neurol. Psychiat.*, **68**, 776-782.
- Greenwood, F. C., Landon, J., and Stamp, T. C. B. (1966). The plasma sugar, free fatty acid, cortisol, and growth hormone response to insulin. 1. In control subjects. *J. clin. Invest.*, **45**, 429-436.
- Gwinup, G. (1965). Test for pituitary function using vasopressin. *Lancet*, **2**, 572-573.
- , Steinberg, T., King, C. G., and Vernikos-Danellis, J. (1967). Vasopressin-induced ACTH secretion in man. *J. clin. Endocr.*, **27**, 927-930.
- Stewart, C. P., Albert-Recht, F., and Osman, L. M. (1961). The simultaneous fluorimetric microdetermination of cortisol and corticosterone in plasma. *Clin. chim. Acta*, **6**, 696-707.
- Teasdale, G. M., Smith, P. A., Wilkinson, R., Latner, A. L., and Miller, H. (1967). Endocrine activity in multiple sclerosis. *Lancet*, **1**, 64-68.
- Wood, J. B., Frankland, A. W., James, V. H. T., and Landon, J. (1965). A rapid test of adrenocortical function. *Lancet*, **1**, 243-245.
- Wynn, V. (1967). The assessment of hypothalamic-pituitary-adrenocortical function in man. *Proc. roy. Soc. Med.*, **60**, 909-910.