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Cushing's syndrome – transitory immune deficiency state?

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Summary: A 28 year old female patient with Cushing's syndrome due to an adrenal adenoma also suffered from recurrent urinary infections (proteus), tonsillitis (streptococcus), permanent candidiasis and perimandibular abscess (*Staphylococcus pyogenes*). Suppression of cellular and humoral immunity was confirmed by *in vitro* tests. After successful right adrenalectomy the clinical signs of Cushing's syndrome disappeared and no evidence of either bacterial or fungal infection were noted one year postoperatively. Immunological tests showed the restitution of both cellular and humoral immunity.

The course of the disease in the patient supports the idea that Cushing's syndrome might be considered as a transitory immune deficiency state.

Introduction

Regardless of origin, hypercortisolaemia, either endogenous or exogenous, suppresses the body's defense apparatus (Craddock, 1978). Both compartments of the immunological system are sensitive to the suppressive effect of corticosteroids (Craddock, 1978). It is well known that patients with Cushing's syndrome are extremely sensitive to various infections (Britton *et al.*, 1975; Hall *et al.*, 1980). The most frequent infections in patients undergoing long-term treatment with pharmacological doses of corticosteroids are: tuberculosis, Staphylococcus, proteus (bacterial), candidiasis and cryptococcus (fungal) (Dale & Petersdorf, 1973).

Case report

A 28 year old woman was admitted to the Haematology Department on 29 July 1982, with a history of hypertension of 9 months duration, with numerous bruises on the skin and muscular weakness. Her blood pressure was as high as 190/130 mm Hg. During the 9 months before admission to hospital she suffered from recurrent urinary infections (*Proteus mirabilis*) and tonsillitis (streptococcus). Two weeks before admission she noticed the appearance of white films on the corners of her lips and tongue and had difficulties in swallowing. There were no menstrual irregularities and 5 years earlier she had given birth to a child.

On admission she presented the classical clinical signs of Cushing's syndrome: truncal obesity, a moon face, a buffalo hump, purple striae and very thin skin. Her weight was 64 kg and height 1.58 m. In the corners of her lips, on tongue, buccal mucosa and throat there were many white areas. The heart rate was 90 per minute. Blood pressure was 190/95 mm Hg. Immediately before admission to hospital she underwent surgical and antibiotic treatment for perimandibular abscess (*Staphylococcus pyogenes* was isolated).

The absence of plasma cortisol diurnal rhythm and non-suppression of plasma cortisol after classical dexamethasone suppression test (Liddle, 1960) confirmed the diagnosis of Cushing's syndrome. Computed tomographic scan, echography and scintigraphy of the adrenal glands were consistent with a right adrenal tumour. Successful right adrenalectomy was performed on 15 February 1983 and the tumour appeared to be a cortical adenoma.

Candida infection disappeared spontaneously after the operation. Repeated urine cultures remained sterile, while no signs of other infections were noted for 2 years after the operation.

Immunological findings

Total white blood cells, granulocytes and eosinophils were normal in the patient during the endogenous overproduction of cortisol (Table I). The percentage of total T lymphocytes measured by E rosettes was low

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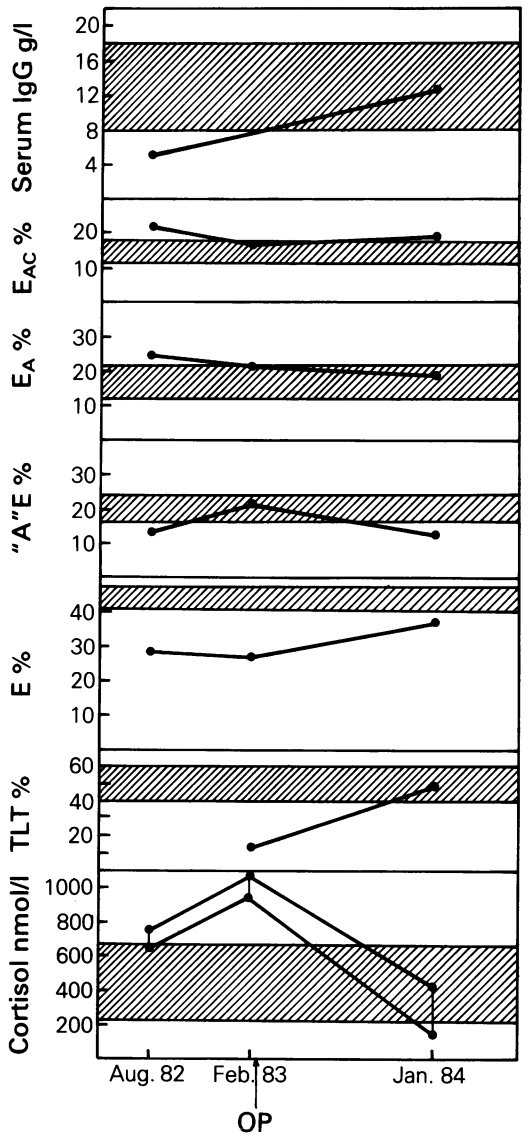

Figure 1 Results of specific analyses before and after surgery. OP = right adrenalectomy; TLT = the lymphoblastic transformation test in the presence of phytohaemagglutinin (PHA) was carried out using the method described by Oppenheim & Schecter (1976). The percentage of present blasts was estimated on a sample of 500 cells. The percentage of T and B lymphocytes was estimated by rosette assay described by Jondal *et al.* (1972). (E – total human T cells; 'A'E – 'active' T cells; E_A – B cells with Fc receptor; E_{AC} – complement binding B lymphocytes).

and there was an inverse relationship between the total number of circulating T lymphocytes and plasma cortisol levels (Figure 1). Both plasma cortisol and the percentage of T lymphocytes returned to normal range after adrenalectomy.

The blastogenic response of T lymphocytes to phytohaemagglutinin (PHA) was drastically reduced (13%) before surgery and after adrenalectomy the lymphocytes regained normal sensitivity to PHA (51%). Serum gamma globulin and immunoglobulin G levels were decreased and returned to within normal range after the operation.

A skin test with purified protein derivative of tuberculin (PPD) was negative before surgery and became positive after adrenalectomy. Thrombocytosis and spontaneous aggregation of platelets were constant findings whilst the patient had Cushing's syndrome. These values were normalized after successful adrenalectomy. Secondary anaemia also disappeared after adrenalectomy.

Discussion

The reduced number of circulating lymphocytes as a result of pharmacological doses of glucocorticoids is due to a redistribution of circulating cells to other body compartments (Fauci & Dale, 1975).

Functional reactivity of T lymphocytes measured by blastogenic response to different antigens (PHA) is suppressed by previous treatment with cortisol (Craddock, 1978). In the study performed by Shohat *et al.* (1979) the functional activity of T lymphocytes, as measured by a local versus host reaction, was normal. The effects of glucocorticoids on subtypes of T cells with either suppressor or helper function awaits a final answer (Nelson & Conn, 1980).

The number of B lymphocytes might be decreased in peripheral blood under the influence of corticosteroids (Yu *et al.*, 1974). Plasma IgA and especially IgG levels are decreased after prolonged treatment with corticosteroids (Butler & Rossen, 1973).

In healthy persons the number of lymphocytes in peripheral blood shows an inverse relationship to the circadian cortisol rhythm. This phenomenon does not exist in patients with Addison's disease but returns after substitution therapy (Thomson *et al.*, 1980).

That long acting hypercortisolaemia significantly suppresses the action of both compartments of the immune system is well known. However, most of the data from the literature are based on studies of the effects of corticosteroid therapy on the immune system (Dale & Petersdorf, 1973; Butler & Rossen, 1973; Yu *et al.*, 1974; Craddock, 1975). There are only a few clinical reports on patients with Cushing's syndrome and proven immune deficiency (Britton *et al.*, 1975).

In the patient reported here the suppression of cellular immunity (decreased total number of peripheral T lymphocytes and decreased blastogenic transformation to PHA) might have been the cause of her

Table I Results of laboratory investigations

	Before surgery	*After surgery*	*Normal values*
White blood cells ($\times 10^9$/l)	5.5 – 8.0	7.3	4.0 – 10.0
Granulocytes ($\times 10^9$/l)	2.9 – 5.1	4.6	2.5 – 6.5
Monocytes ($\times 10^9$/l)	0.2 – 0.6	0.5	0.2 – 0.5
Eosinophils ($\times 10^9$/l)	0.06– 0.15	0	0.08– 0.25
Lymphocytes ($\times 10^9$/l)	1.5 – 2.9	2.2	1.0 – 3.0
Haemoglobin (g/l)	66 –110	114	120 –160
Erythrocytes ($\times 10^{12}$/l)	2.1 – 3.6	3.6	3.75– 5.0
Platelets ($\times 10^9$/l)	187 –620	190	150 –350
Total serum protein (g/l)	53	71	65 – 80
serum albumin (g/l)	34.9	41.2	36.4 – 44.8
serum gamma globulin (g/l)	4.2	14.2	10.1 – 17.4
IgA (g/l)	1.2	1.8	0.9 – 4.5
IgM (g/l)	1.0	2.2	0.6 – 2.8
IgG (g/l)	5.2	12.2	8.0 – 18.0

chronic candida infection and the suppression of humoral immunity (decreased concentration of IgG) the cause of her frequent and serious bacterial infections. The recovery of the patient's immune system occurred after the definitive cure of Cushing's syndrome.

Our data, together with some data from the literature here presented, support the idea that Cushing's syndrome might be considered as a transitory immune deficiency state.

References

BRITTON, S., THOREN, M. & SJOBERG, H.E. (1975). The immunological hazard of Cushing's syndrome. *British Medical Journal*, **4,** 678.

BUTLER, W.T. & ROSSEN, R.D. (1973). Effects of corticosteroids on immunity in man. I. Decreased serum IgG concentrations caused by 3 or 5 days of high doses of methylprednisolone. *Journal of Clinical Investigation*, **52,** 2629.

CRADDOCK, C.G. (1978). Corticosteroid-induced lymphopenia, immunosuppression and body defence. *Annals of Internal Medicine*, **88,** 564.

DALE, D.C. & PETERSDORF, R.G. (1973). Corticosteroids and infectious diseases. *Medical Clinics of North America*, **57,** 1277.

FAUCI, A.S. & DALE, D.C. (1975). The effect of hydrocortisone on the kinetics of normal human lymphocytes. *Blood*, **46,** 235.

HALL, R., ANDERSON, J., SMART, G.A. & BESSER, G.M. (1980). In *Fundamentals of Clinical Endocrinology*, 3rd edition, p. 244. Pitman Medical: London.

JONDAL, M., HOLM, G. & WIGZELL, H. (1972). Surface markers on human T and B lymphocytes I. A large population of lymphocytes forming nonimmune rosettes with sheep blood cells. *Journal of Experimental Medicine*, **136,** 207.

LIDDLE, G.W. (1960). Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. *Journal of Clinical Endocrinology and Metabolism*, **20,** 1539.

NELSON, A.M. & CONN, D.L. (1980). Glucocorticoids in rheumatic disease. *Mayo Clinic Proceedings*, **55,** 758.

OPPENHEIM, J.J. & SCHECTER, B. (1976). Lymphocyte transformation. In *Manual of Clinical Immunology*, Rose, N.R. & Friedman, H. (eds). American Society: Washington.

SHOHAT, B., KLEIN, A., KAUFMAN, H., BLUM, I. & CHOWERS, I. (1979). T lymphocytes and plasma inhibitory factor in ACTH-dependent Cushing's patients. *Clinical Immunology and Immunopathology*, **13,** 452.

THOMSON, S.P., McMAHON, L.J. & NUGENT, C.A. (1980). Endogenous cortisol: a regulator of the number of lymphocytes in peripheral blood. *Clinical Immunology and Immunopathology*, **17,** 506.

YU, D.T.Y., CLEMENS, P.J., PAULUS, H.E., PETER, J.B., LEVY, J. & BARNETT, E. (1974). Human lymphocyte subpopulations: effects of corticosteroids. *Journal of Clinical Investigation*, **53,** 565.