Hypothalamo-pituitary-adrenal function in intrinsic non-atopic asthma

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Collins, J. V., Bellamy, D., Britton, M. G., Townsend, J., and Brown, D. J. (1975). *Thorax*, 30, 578–581. **Hypothalamo-pituitary-adrenal function in intrinsic non-atopic asthma.** Sixteen patients with intrinsic non-atopic asthma with persistent wheezing who had never been treated with corticosteroids showed normal adrenocortical responses to prolonged stimulation with Tetracosactin Depot. In a subgroup of six patients the hypothalamo-pituitary-adrenal (HPA) response to a standard insulin stress test was normal. It is concluded that impaired responsiveness of the HPA axis is unlikely to be a common factor in initiating or maintaining airways obstruction in patients with intrinsic asthma.

The relationship of adrenocortical function and bronchial asthma has long been the subject of controversy (Editorial, 1965). Enhancement of bronchial hypersensitivity in guinea-pigs following adrenalectomy was reported by Képinov (1922), and Rackemann (1945) found low urinary 17-keto steroid excretion in one patient with asthma. Bronchial asthma may rarely be a presenting feature in Addison's disease (Green and Lim, 1971). Earlier reports from different authors of studies of adrenocortical function in asthma showed discrepancies which may have resulted from variations in the methods and accuracy of the hormonal assay employed. An association between intrinsic asthma and sub-normal adrenocortical function has been suggested (Robson and Kilborn, 1965). The present study examines hypothalamo-pituitary-adrenal (HPA) function in patients with intrinsic non-atopic asthma.

PATIENTS AND METHODS

Twenty patients with bronchial asthma were studied after admission to hospital for a trial of corticosteroids because of poor control of symptoms. Each patient had suffered persistent and, in some cases, continuous wheezing since the onset of asthma but had never been treated with adrenal stimulation or corticosteroids. At the time of the studies each patient had clinical

and spirometric evidence of airways obstruction but none had significantly abnormal blood gas tensions. All patients gave informed consent to the studies.

In all patients the blood eosinophil count was in excess of 500/mm³ and the sputum eosinophil count was 40% or more. Sixteen patients were classed as intrinsic non-atopic asthmatics because they had no history of hypersensitivity and showed no immediate or delayed reactions to skin prick tests with a range of 23 common allergens (see Appendix). The four remaining patients who were classed as extrinsic atopic subjects showed significant positive immediate reactions to two or more common allergens and reported symptoms related to exposure to house dust, pollens or domestic pets.

All studies were begun between 8.00 and 10.00 am with the patient semirecumbent after an overnight fast. Blood samples for estimation of plasma cortisol levels were obtained through an indwelling venous cannula inserted into forearm vein one hour before the start of the study. Blood samples were centrifuged immediately, and plasma was stored at 4°C until cortisol levels were estimated, using a modification of the method of Mattingley (1962). Each sample was analysed in duplicate.

In six of the intrinsic non-atopic patients a standard insulin stress test was performed on the first day using a single intravenous injection of

soluble insulin, 0.15 unit per kg body weight. On the second day in these patients and in all the remaining patients a prolonged Synacthen (Tetracosactin) stimulation test was performed with an intramuscular injection of 1 mg Synacthen Depot.

RESULTS

Statistical analyses of clinical and laboratory details for the two groups of patients are shown in Table I and for the responses to Synacthen stimulation tests and insulin stress tests are shown in Tables II and III.

Using *t*-statistics for unequal variances the results of the Synacthen stimulation tests in the 16 patients with intrinsic asthma were compared with values obtained in 107 normal subjects (Ciba), and the results of the insulin stress

tests were compared with values for 12 normal subjects reported by Landon, Wynn, and James (1963). In every patient there was a brisk and sustained rise in plasma cortisol level in response to Synacthen with an increment above the resting level of at least 200 nmol/l at 30 minutes after injection. The mean and SD of the increment for the patients with intrinsic asthma (460 ± 174 nmol/l) were not significantly different from those for normal subjects (457 ± 223 nmol/l). The plasma cortisol levels for the intrinsic asthmatics were significantly higher ($P < 0.05$) than for normal subjects at each interval to five hours after injection of Synacthen. Moreover in seven of these patients in whom levels were measured at 8 and 24 hours after injection there was evidence of a sustained response to stimulation (see Table II). Similar

TABLE I
CLINICAL DETAILS OF PATIENTS WITH ASTHMA

	Age (yr)	Duration of Asthma (yr)	Sputum Eosinophilia %	Blood Eosinophilia $\times 10^6/l$
16 intrinsic patients				
Mean	51.3	9.6	63.1	0.790
SD	11.5	7.6	11.8	0.256
SEM	2.9	1.9	3.0	0.065
4 extrinsic patients				
Mean	28.8	18.5	56.3	0.770
SD	14.5	18.7	8.5	0.146
SEM	7.3	9.4	4.3	0.074

TABLE II
PLASMA 11-HYDROXYCORTICOSTEROID (11-OHCS) LEVELS AFTER INJECTION OF 1 mg SYNACTHEN DEPOT

Hours	Plasma 11-OHCS (nmol/l) after Synacthen								
	0	$\frac{1}{2}$	1	2	3	4	5	8 ¹	24 ¹
16 intrinsic patients									
Mean	377	840	1085	1209	1336	1435	1512	1526	1449
SD	121	184	322	220	245	215	245	253	160
SEM	30	47	80	55	61	55	61	66	41
4 extrinsic patients									
Mean	408	848	1102	1226	1358	1399	1460	1736	1424
SD	138	132	149	83	113	185	251	482	413
SEM	69	66	74	41	58	94	127	242	207

¹Number of intrinsic subjects = 7.

TABLE III
SIX PATIENTS WITH INTRINSIC ASTHMA: PLASMA 11-OHCS LEVELS FOLLOWING IV INJECTION OF SOLUBLE INSULIN 0.15 μ g/kg BODY WEIGHT

INSULIN 0.15 mg/kg BODY WEIGHT								
	Lowest Blood Sugar (mmol/l)	Plasma 11-OCHS Levels (nmol/l)						Maximum Increment
		Minutes after iv insulin						
		0	30	45	60	90	120	
Mean	1.43	388	477	743	804	868	865	587
SD	0.31	157	129	99	96	171	240	196
SEM	0.12	63	52	41	39	69	96	80

results were obtained for the four patients with extrinsic asthma but the small numbers made statistical comparisons less valid. The insulin stress test in six patients with intrinsic asthma showed normal responses. In every patient the blood sugar level fell below 2.22 mmol/l, the maximum plasma cortisol exceeded 550 nmol/l, and the increment above the basal level was at least 275 nmol/l. The mean and SD for the maximum increment was 587 ± 196 nmol/l in patients with asthma compared with 353 ± 102 nmol/l in normal subjects.

DISCUSSION

In the present study adrenocortical function was normal in patients with extrinsic asthma, and this agrees with previous reports (Blumenthal *et al.*, 1966; Weller *et al.*, 1968). Weller *et al.* (1968) found that cortisol production rates were normal in patients with extrinsic asthma in the ambulant state but were diminished at rest. The adrenal response to ACTH infusions was normal in their patients but the response to pyrogen stimulation tests was slightly but significantly impaired. Robson and Kilborn (1965) studied patients with continuous asthma and inferred from the experience of Ogilvie (1962) that their asthma was intrinsic in type. In these patients, cortisol production rates were normal at rest but the response to ACTH stimulation was impaired in 68%. There was an inverse relationship between the duration of symptoms and the response to ACTH. Both Weller *et al.* (1968) and Robson and Kilborn (1965) discussed the possibility that adrenocortical insufficiency may precede or result from the effects of asthma. The association of asthma with Addison's disease appears to be uncommon in the absence of previous steroid treatment (Carrier, Sherrick, and Gastineau, 1960; Green and Lim, 1971). Similarly, in patients admitted to hospital with status asthmaticus signs of hypoadrenalism are uncommon even in patients who have received previous treatment with corticosteroids (Cayton and Howard, 1973). Adrenal atrophy has rarely been recorded in patients dying of asthma in the absence of previous steroid treatment (Speizer *et al.*, 1968; Green and Lim, 1971; Fraser *et al.*, 1971). Airways obstruction of itself does not seem to be associated with impaired adrenocortical function, for in patients with chronic bronchitis and severe fixed airways obstruction Weston and Kind (1969) found normal adrenocortical responses to ACTH.

The present study has failed to show any rela-

tionship between intrinsic non-atopic asthma and impairment of HPA responses. There was no evidence that increasing age or duration of asthma affected the adrenocortical response to stimulation by stress or Synacthen. The plasma cortisol levels recorded in our patients were higher than those previously reported for normal subjects using the same assay methods (Ciba; Landon *et al.*, 1963). This suggests that in patients subjected to the stimulus of persistent asthma adrenal mass may be increased, as has been reported in patients dying with cardiovascular diseases and malignant neoplasms (Studzinski, Hay, and Symington, 1963). Examination of reports of necropsy findings in patients dying of asthma has failed to reveal details of adrenal size in most patients (Houston, Nevasquez, and Trounce, 1953; Speizer *et al.*, 1968).

It seems unlikely that impaired responsiveness of the HPA axis is an important or common factor in precipitating or maintaining airway obstruction in patients with asthma except where previous corticosteroid treatment has resulted in suppression. Clinical experience of the efficacy of supraphysiological plasma levels of cortisol or synthetic substitutes in the treatment of asthma may have resulted in an over-emphasis of the role which impaired HPA responses play in asthma.

APPENDIX

All patients were tested for hypersensitivity by standard prick test with the following solutions produced by Bencard Ltd:

Control, house dust, *Dermatophagoides pteronyssinus*, grass pollen, shrub pollens, tree pollens, cat fur, dog hair, horse hair, feathers mixed, pigeon feathers, budgerigar feathers, alternaria, *Aspergillus fumigatus*, Cladosporium dry rot, Sporobolomyces, yeast, *Candida albicans*, milk, eggs, wheat, fish, nuts.

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