EXTENDED REPORT

Hypothalamic-pituitary-adrenal axis function in ankylosing spondylitis

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Objective: To assess basal function and responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis in patients with ankylosing spondylitis during dynamic testing.

Methods: Insulin induced hypoglycaemia (IIH) (Actrapid HM 0.1 IU/kg, as intravenous bolus) was induced in 17 patients and 11 healthy controls matched for age, sex, and body mass index. Concentrations of glucose, adrenocorticotrophic hormone (ACTH), cortisol, insulin, dehydroepiandrosterone sulphate (DHEAS), 17 α -hydroxyprogesterone, interleukin 6 (IL-6), and tumour necrosis factor α (TNF α) were determined in plasma.

Results: Comparable basal cortisol levels were found in the two groups, with a trend to be lower in ankylosing spondylitis. In the ankylosing spondylitis group, there were higher concentrations of IL-6 (mean (SEM): 16.6 (2.8) pg/ml v 1.41 (0.66) pg/ml in controls; $p < 0.001$) and TNF α (8.5 (1.74) pg/ml v 0.08 (0.42) pg/ml in controls; $p < 0.01$). Glucose, insulin, ACTH, DHEAS, and 17 α -hydroxyprogesterone did not differ significantly from control. The IIH test was carried out successfully in 11 of the 17 patients with ankylosing spondylitis, and the ACTH and cortisol responses were comparable with control. General linear modelling showed a different course of glycaemia ($p = 0.041$) in the ankylosing spondylitis patients who met the criteria for a successful IIH test compared with the controls.

Conclusions: The results suggest there is no difference in basal HPA axis activity and completely preserved responsiveness of the HPA axis in patients with ankylosing spondylitis. The interpretation of the different course of glycaemia during IIH in ankylosing spondylitis requires further investigation.

Ankylosing spondylitis is a rheumatic disorder which typically affects the sacroiliac joints and the spine. It belongs to the group of spondylarthropathies with a higher prevalence in men. A strong association with the major histocompatibility complex class I molecule HLA B-27, together with hereditary, environmental, and other factors including endocrine perturbations, may operate in the pathogenesis of ankylosing spondylitis.¹ Detailed relations are, however, still unclear.

During the past decade data have accumulated suggesting a role for the neuroendocrine system in the pathogenesis of rheumatic diseases. Studies in patients with rheumatoid arthritis broadly support the hypothesis that the hypothalamic-pituitary-adrenal (HPA) axis plays a critical role in counterregulation of immune inflammatory processes. Thus dysregulation of the HPA axis response is likely to predispose individuals to the onset of chronic inflammatory diseases including ankylosing spondylitis, or to affect their severity.^{2–3} In contrast to rheumatoid arthritis, few published reports have addressed HPA axis activity in ankylosing spondylitis.

The activity of the HPA axis is regarded as inappropriately normal with respect to the ongoing inflammation in rheumatoid arthritis.⁴ Decreased HPA axis activity seems to result from relative adrenal insufficiency, as reported in a subset of younger women with rheumatoid arthritis.^{5,6} In general, basal levels of adrenal glucocorticoids, particularly morning cortisol concentrations < 100 nmol/l in plasma, may reflect significant adrenal insufficiency.⁷ However, subtle degrees of glucocorticoid deficiency tend to be obscured by negative feedback control of the HPA axis. Low levels of adrenal androgen dehydroepiandrosterone sulphate (DHEAS) in women with premenopausal onset rheumatoid arthritis have been regarded as markers of adrenal hypo-competence or insufficiency,⁸ while conflicting DHEAS results have been reported in ankylosing spondylitis.^{1–9,10}

Based on the available cross sectional data, it cannot be clearly assessed whether the overall activity of the HPA axis is changed in ankylosing spondylitis. Thus dynamic tests of HPA axis function, such as insulin induced hypoglycaemia (IIH), would shed more light on HPA function. IIH stimulates the neuroendocrine response at a suprahypothalamic level. This provides an opportunity to assess the response of the HPA axis at both pituitary and adrenal level.¹¹ A drawback of the IIH test is that subjects with insulin resistance that is not clinically apparent could have an inadequate decrease in glycaemia, which may be insufficient to trigger a neuroendocrine response.

Our present study was designed to investigate the activity of the HPA axis in the basal state and during hypoglycaemic stimulation. Owing to an unexpected occurrence of insulin resistance the ankylosing spondylitis patients were divided into two subgroups with normal and high insulin resistance, respectively.

METHODS

We studied 17 patients fulfilling the criteria of the European Spondylarthropathy Study Group of Ankylosing Spondylitis, recruited from the National Institute for Rheumatic Diseases in Piestany, Slovakia. Eleven healthy subjects matched for age, sex, and body mass index served as controls. None of the patients or controls had a history of diabetes or impaired glucose tolerance. The disease activity of the patients, evaluated by the erythrocyte sedimentation rate, was mild to moderate. The characteristics of all the subjects and controls are shown in table 1. None of the patients had been treated previously with glucocorticoids. Treatment consisted of

Abbreviations: DHEAS, dehydroepiandrosterone sulphate; HPA, hypothalamic-pituitary-adrenal; IIH, insulin induced hypoglycaemia; 17-OHP, 17 α -hydroxyprogesterone

methotrexate ($n = 3$; mean length of treatment 6.5 months), sulphasalazine ($n = 7$; mean length of treatment 25.6 months), and other non-steroid anti-inflammatory drugs (NSAID) ($n = 12$; mean length of treatment 108.7 months). To minimise the effect of treatment with NSAID on HPA axis activity, the last drug dose was 24 hours before the investigation.

All subjects gave their informed written consent, and the study was approved by the ethics committee of the National Institute of Rheumatic Diseases.

The investigations started at 08:00 hours after an overnight fast. An indwelling catheter was inserted into the cubital vein for blood sampling. The first blood sample was taken 30 minutes after inserting the catheter. An intravenous injection of insulin (0.1 IU/kg, Actrapid HM, Novo Nordisk A/S Bagsvaerd, Denmark) was given afterwards. At the intervals shown in fig 1, blood samples were collected into polyethylene tubes containing EDTA or heparin as anticoagulants and immediately cooled. After centrifugation plasma aliquots were stored at -20°C until analysed. Concentrations of cortisol, adrenocorticotrophic hormone (ACTH), DHEAS, 17α -hydroxyprogesterone (17-OHP), insulin, and interleukin 6 (IL-6) were assayed by immunoradiometric assay (IRMA) (Immunotech SA, Marseille, France), and tumour necrosis factor α (TNF α) by enzyme linked immunosorbent assay (ELISA) (Immunotech). Plasma glucose concentrations were analysed by the glucose oxidase method.

Insulin resistance was estimated by the homeostasis model insulin resistance index (HOMA-IR) using the formula: fasting plasma glucose (mmol/l) multiplied by fasting insulin ($\mu\text{IU/ml}$) divided by 22.5.¹² Based on the HOMA-IR index calculated for each patient, the ankylosing spondylitis group was dichotomised into two subgroups: subgroup 1 (AS1; $n = 11$) with HOMA-IR lower than the mean +2 SD HOMA-IR in controls (that is, 4.36), and subgroup 2 (AS2; $n = 6$) with HOMA-IR higher than the mean +2 SD HOMA-IR in controls.

Statistics

Statistical evaluation was carried out using the SIGMASTAT 2.0 program (Jandel Scientific, San Rafael, California, USA) and SPSS 10.0 (SPSS Inc, Chicago, Illinois, USA). Comparisons of basal hormone and cytokine concentrations were evaluated by Mann-Whitney rank sum test. The general linear model (multiple analysis of variance module) was used to determine the differences in endocrine response during IHH between patients and controls, the differences from the baseline within each group, and the respective interactions. All data are expressed as mean (SEM) unless indicated. Significance was set at $p < 0.05$.

RESULTS

The mean basal concentrations at approximately 08:30 hours of plasma glucose, hormones, and cytokines analysed in the study are shown in table 2. The fasting plasma glucose levels

Table 1 Basic characteristics of the patients with ankylosing spondylitis and their subgroups, and of the healthy controls

	AS	AS1	AS2	Controls
Number of subjects	17	11	6	11
Age (years)	40.5 (1.8)	39.5 (1.4)	42.3 (4.5)	40.1 (2.2)
Sex (M/F)	14/3	9/2	5/1	8/3
BMI (kg/m^2)	25.1 (1.1)	23.5 (0.17)	27.1 (2.4)	23.1 (1.0)
Disease duration (years)	9.1 (1.6)	10.1 (2.1)	7.2 (2.7)	–

Values are expressed as mean (SEM). Statistical significance was set at $p < 0.05$.

AS, ankylosing spondylitis; AS1, subgroup with normal insulin resistance; AS2, subgroup with increased insulin resistance; BMI, body mass index.

Figure 1 Concentrations of glucose (top), adrenocorticotrophic hormone (ACTH) (middle), and cortisol (bottom) in plasma of the AS1 subgroup of patients and the healthy controls during insulin induced hypoglycaemia. Data are means, error bars = SEM. Asterisks indicate the level of statistical significance between AS1 and control groups assessed by the general linear model at time 0 min v 15 min (* $p = 0.002$) and at time 45 min v 60 min (** $p = 0.031$). AS1, ankylosing spondylitis subgroup with normal insulin resistance.

were within the physiological range in all subjects except one AS2 patient. The concentration of fasting glucose measured in plasma of AS1 patients was similar to that in healthy controls, while plasma glucose in AS2 patients was higher than in the controls ($p = 0.03$). Five patients (29%), all belonging to the AS2 subgroup, and none of the controls had raised basal insulin levels ($>20 \mu\text{IU/ml}$) after an overnight fast. All controls had HOMA-IR below 4.36. Owing to the dichotomisation of the ankylosing spondylitis group into AS1 and AS2, both the mean insulin levels and HOMA-IR were higher ($p < 0.001$) in the AS2 patients, but not in the AS1 patients, than in the controls.

The mean basal cortisol concentrations in plasma in the patients tended to be lower than in the controls, but the

difference did not reach statistical significance ($p = 0.063$). We did not find any significant correlation between the cortisol levels and disease duration; length of methotrexate treatment; length of sulphasalazine treatment; or length of other NSAID treatment. The mean basal ACTH concentrations were similar in the patients and the controls, as were the mean concentrations of 17-OHP and DHEAS. No significant differences in the basal levels of cortisol, ACTH, DHEAS, or 17-OHP were observed between controls and the AS1 and AS2 subgroups. As expected, plasma IL-6 was significantly higher ($p < 0.001$) than control in the patient group as a whole and also in the AS1 and AS2 subgroups. Concentrations of TNF α were raised ($p < 0.01$) in the whole patient group and in the AS1 subgroup, though the values in the AS2 subgroup were comparable with those in the controls. There was no significant correlation between either IL-6 or TNF α and basal levels of the hormones measured.

Insulin administration resulted in a decrease ($p < 0.001$) in plasma glucose concentrations in both AS2 (data not shown) and AS1 subgroups, as well as in the controls (fig 1). However, all AS2 patients had an insufficient decrease in plasma glucose levels ($>50\%$ of basal values) and thus they did not meet the criteria of a successful IIH test.¹¹ Insulin administration was followed by significant ($p < 0.001$) changes in plasma glucose in both AS1 and control groups. The general linear model test showed differences in the course of the changes of plasma glucose in AS1 patients ($F = 5.484$, $p = 0.041$) compared with the controls. The changes in glycaemia at time 0 v 15 minutes were also significantly different ($F = 16.4$, $p = 0.002$) in AS1 patients compared with the controls, as were the changes between 45 and 60 minutes ($F = 6.3$, $p = 0.031$). The nadir occurred 30 minutes after the insulin bolus and represented approximately 39% of the basal concentration in AS1 patients, 54% in AS2 patients, and 33% in the controls.

IIH resulted in a rise ($p < 0.001$) in mean plasma ACTH concentration, from 14.3 (1.8) pg/ml at time zero to 92.8 (17) pg/ml at 45 minutes in the AS1 group, and from 13.3 (1.7) pg/ml to 85.3 (16.3) pg/ml at 45 minutes in the controls. Neither

the mean basal plasma ACTH concentrations nor the response of plasma ACTH to hypoglycaemia in the AS1 group differed from control (fig 1).

Circulating cortisol concentration during IIH increased in both AS1 and control groups between 15 minutes and 30 minutes ($p < 0.05$) and between 30 minutes and 45 minutes ($p < 0.001$). The response of cortisol during IIH did not differ significantly between AS1 patients and controls ($F = 1.61$, $p = 0.232$) (fig 1). As shown in table 1, the increment of cortisol over the interval from time zero to 60 minutes (Δ cortisol 60-0) in the AS1 group was slightly higher than in the controls ($p = 0.14$).

DISCUSSION

In this study we investigated the endocrine profile of patients with ankylosing spondylitis. We also carried out dynamic testing of neuroendocrine responsiveness to IIH in order to evaluate the activity of the HPA axis in patients with this condition.

We found basal ACTH and cortisol levels to be similar in the patients with ankylosing spondylitis and the controls, with a tendency for cortisol to be lower in the patients. Although this observation by itself might imply a slightly decreased ability of the adrenal glands to respond to the ACTH stimulus or suggest a changed sensitivity to feedback signals within the HPA axis, the cortisol response to ACTH during IIH indicated a completely preserved function of the adrenals, at least in subgroup AS1 (fig 1). The difference in the basal cortisol levels could also be explained by a higher degree of anticipatory stress before the investigation in control subjects, or by previous treatment with NSAID in the patients with ankylosing spondylitis. However, we did not find any significant correlation between the basal cortisol levels and the length of treatment with the drugs taken by the patients. Chikanza and colleagues showed corticosteroid responses appropriate to the degree of the inflammatory disease in patients with ankylosing spondylitis with low circulating levels of ACTH and high arginine vasopressin.¹³

Concentrations of DHEAS, a weak adrenal androgen, have been found to be normal in 25 patients with various spondylarthropathies, including ankylosing spondylitis.¹⁴ Other investigators observed lower DHEAS levels in both male and female patients with spondylarthropathies⁹ and ankylosing spondylitis.¹⁰ Significantly raised DHEAS levels were even reported in 50 male patients with ankylosing spondylitis.¹ In our study, however, we found that the DHEAS levels in the patients with ankylosing spondylitis were comparable with those in the control group.

We did not observe any significant difference in mean 17-OHP levels in our patients with ankylosing spondylitis compared with the controls. In a previous study,¹⁵ the serum level of 17-OHP, an important product of the adrenals, was significantly increased in male patients with ankylosing spondylitis when pooled with other spondylarthropathies. In another study, only a non-significantly increased level of 17-OHP was reported.¹⁶ Giltay *et al* suggested that the increase in 17-OHP and DHEAS levels in ankylosing spondylitis might be a consequence of the chronic inflammatory disease, reflecting a generalised stress response or partial, subclinical 11 β - or 21-hydroxylase deficiency.¹ A significantly higher response of 17-OHP in a low dose ACTH test has been reported in patients with polymyalgia rheumatica.¹⁷

Although slightly lower basal cortisol levels might reflect a moderate inhibition of the HPA axis, the results of dynamic testing, along with normal basal DHEAS and 17-OHP levels, did not indicate adrenal insufficiency in the AS1 patients. Despite the presence of inflammatory activity indicated by raised levels of IL-6 and TNF α found in ankylosing

Table 2 Fasting concentrations of glucose, hormones, and interleukins in plasma in all patients with ankylosing spondylitis and the AS1 and AS2 subgroups, and in healthy controls, at approximately 08.30 hours after an overnight fast

	AS	AS1	AS2	Controls
Glucose (mmol/l)	5.27 (0.18)	4.97 (0.09)	5.83 (0.428)*	5.02 (0.11)
Insulin (μ U/ml)	14.03 (3.59)	4.79 (0.52)	30.9 (5.22)***	7.54 (1.66)
HOMA-IR	3.52 (0.97)	1.07 (0.12)	8.01 (1.51)***	1.72 (1.32)*
Cortisol (nmol/l)	382 (47)	371 (63)	403 (73)	511 (37)
Δ Cortisol 60-0†	—	346.5 (60.7)	—	207 (79.8)
ACTH (pg/ml)	13.9 (1.9)	14.3 (8.6)	13.1 (2.3)	14.1 (1.8)
17-OHP (ng/ml)	1.04 (0.21)	0.85 (0.12)	1.37 (0.57)	1.23 (0.22)
DHEAS (μ mol/l)	5.05 (0.70)	5.07 (0.60)	5.01 (1.80)	5.06 (0.60)
IL-6 (pg/ml)	16.6 (2.8)***	19.1 (2.2)***	12.1 (3.5)***	1.41 (0.66)
TNF α (pg/ml)	8.5 (1.74)**	10.2 (2.6)**	5.42 (0.51)	4.08 (0.42)

Values are mean (SEM).

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

†Change in cortisol between baseline and 60 minutes.

ACTH, adrenocorticotrophic hormone; AS, ankylosing spondylitis; AS1, subgroup with normal insulin resistance; AS2, subgroup with increased insulin resistance; DHEAS, dehydroepiandrosterone sulphate; HOMA-IR, homeostasis model insulin resistance index; IL-6, interleukin 6; TNF α , tumour necrosis factor α ; 17-OHP, 17 α -hydroxyprogesterone.

spondylitis in our study, as well as by other investigators,¹⁸ we did not observe a significant reduction in the HPA axis response, in contrast with findings in other inflammatory diseases such as rheumatoid arthritis.^{5, 19}

Dynamic testing of the neuroendocrine response by IHH provides the possibility of studying sympatho-neural, sympatho-adrenal, adeno-pituitary, and adrenal functions. The basic condition to trigger the neuroendocrine response is an adequate decrease in plasma glucose level following intravenous insulin administration. An inadequate decrease in glucose levels found in the AS2 subgroup restricted the interpretation of the IHH results in those patients. Overweight is a well known factor that markedly influences insulin resistance.²⁰ The decreased sensitivity to the administered insulin found in the AS2 subgroup, together with increased insulin resistance estimated by the HOMA-IR index, was therefore probably a result of a higher BMI index compared with the controls or the AS1 subgroup.

In the present study we found a significantly different course of glycaemia in the patients in the AS1 subgroup, who had a BMI and HOMA-IR comparable with the healthy controls. As shown in fig 1, the AS1 patients had a trend to a slower decrease in glycaemia during first 15 minutes of IHH and a faster recovery of plasma glucose to normoglycaemic values in the latter phase of IHH (60 to 90 minutes) compared with the controls. It can be hypothesised that insulin had a slightly altered action on peripheral tissues owing to a degree of insulin resistance causing a slower decrease in glycaemia in the AS1 subgroup, or that insulin had insufficiently blocked the hepatic glucose output. Several investigators have reported various disorders of glucose handling in chronic inflammatory diseases.^{21–23} Moreover, an increased insulin response during an oral glucose load indicating insulin resistance has been observed in patients with ankylosing spondylitis.²⁴

Alternatively, the different course of glycaemia during the latter phase of IHH might be attributed to a faster and more intense counterregulatory response. However, it seems unlikely that glucose levels would be significantly affected by counterregulatory hormones, particularly adrenaline and glucagon, during the first 15 minutes after insulin administration.²⁵ On the basis of the present data the mechanisms operating in the altered insulin action in the AS1 subgroup of patients cannot be clearly addressed, and further investigations will be required.

Conclusions

No significant difference in basal levels of ACTH, cortisol, 17-OHP, or DHEAS was found between patients with ankylosing spondylitis and controls. The tendency for cortisol to be slightly lower in ankylosing spondylitis might reflect previous treatment with NSAID or greater anticipatory stress in control subjects. The responsiveness of the HPA axis on pituitary and adrenal levels seems to be completely preserved, at least in the AS1 subgroup of patients without fasting signs of insulin resistance. A significantly different course of glycaemia both in the first and in the later phase of IHH was observed in the AS1 subgroup of patients without fasting signs of insulin resistance. Interpretation of these results will require further investigations.

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