Polymyalgia rheumatica: Evidence for a hypothalamic-pituitary-adrenal axis-driven disease

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Key words: HPA, polymyalgia rheumatica, DHEAS, cortisol.

Introduction

During the recent First International Conference on Polymyalgia Rheumatica (PMR) several pathogenic and clinical aspects of this disease were discussed and it became clear that some of them might well overlap with rheumatoid arthritis (RA), or at least with elderly onset RA (EORA) (1). The potentially overlapping signs and symptoms include the female to male preponderance, synovitis, involvement of the Th1 cytokines, the presence of activated monocytes/macrophages in the pathological lesions, a common association with the HLA-DRB1 alleles, the role played by infectious agents, the favourable effects of combination therapies with steroids plus methotrexate, antimalarials or azathioprine, and the frequent elderly onset (1). However, the pathogenesis of PMR remains speculative.

On the other hand, in recent years neuroendocrine immune mechanisms have been shown to play a significant role among the factors involved in the pathogenesis of RA (2). Since there are many pathogenetic similarities between PMR and EORA, it may be hypothesized that alterations of the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-gonadal (HPG) axis could also play an important role in the pathogenesis of PMR.

The abrupt onset of the disease and the dramatic and rapid disappearance of PMR following corticosteroid administration are reminiscent of both the steroid withdrawal syndrome (i.e., myalgia, malaise, fever, pain, depression, sleepiness, anorexia etc.) and the mild to moderate crises of adrenocortical insufficiency.

Here we would like to report and discuss some of the existing evidence which suggests that alterations of the HPA axis could represent important features of PMR.

Immunosenescence and endocrinosenescence: A possible basis for PMR development?

It is an acknowledged fact that the immune system influences the endocrine system and vice versa. The modulation of the endocrine system by the immune system has been demonstrated in animal models by the marked change in the HPA axis activity induced by the injection of antigenic stimuli or cytokines (3). At the same time, hormones of the endocrine system can modulate immune functions — for example, the well known inhibition of cytokines by cortisol, estrogens, testosterone and dehydroepiandrosterone (DHEA) (4) (Fig. 1). Therefore, the two systems are closely linked, and the aging of one system necessarily involves the aging of the other system (4).

With respect to the innate immune system, a loss of phagocytic capacity, the decreased generation of radicals (neutrophils), and an increase in “early” cytokines (IL-6, TNF) have been demonstrated during aging (5).

With respect to the aging of the endocrine system, the decline of adrenal/gonadal hormones differs between the sexes in healthy subjects. For example, cortisol and 17-hydroxyprogesterone decrease in female subjects, but not in male subjects (4). In both sexes cortisol serum levels are relatively low in relation to plasma adrenocorticotropic hormone (ACTH), which indicates that — despite increased ACTH — the production of cortisol decreases during aging. However, cortisol serum levels remain relatively high in relation to the serum levels of other adrenal and gonadal hormones during aging (4).

These changes could constitute prerequisites for the development of age-related diseases such as PMR, EORA, osteoporosis, late-onset B cell malignancies, atherosclerosis, and other conditions in which IL-6 in particular may play a pathogenic role. As a matter of fact, in these diseases and during aging, a decrease in adrenal hormones such as DHEA is believed to play an important facilitating role in IL-6-mediated pathogenic effects. Serum DHEA, DHEA sulphate (DHEAS) and androstenedione (ASD) levels were recently reported to be significantly decreased with age, whereas serum IL-6 levels were reported to be significantly increased (6). In this study, it was also demonstrated that DHEA and ASD have a direct inhibitory effect on IL-6 secretion in monocytes and macrophages (6). These findings support a link between immunosenescence and endocrinosenescence. An earlier study show-
ing low serum DHEAS levels in PMR patients not treated with corticosteroids also confirms the presence of low levels of this adrenal hormone in RA patients (7, 8).

The role of the hypothalamic-pituitary-adrenal axis in PMR

Although one of the most striking features of PMR is the development of the disease in patients older than 50 years of age, the precise age-associated pathogenic factors are not yet known. The age-specific incidence rate increases from 2.6 per 100,000 in the age group 50-59 years to 44.7 per 100,000 in the age group 80 years and older, which strongly suggest the possibility of age-associated factors in etiology.

The natural decline in several hormones, including DHEA and ADS during aging may well represent one such factor (4, 6, 9). A recent study has partially clarified this point, by analyzing the interrelationship between inflammatory cytokines (IL-6, TNF) and adrenal hormones (cortisol, DHEAS, ADS) in more than 100 PMR patients with both recent onset and chronic disease (10). As expected, IL-6 levels were significantly higher in early PMR patients as compared to age-matched normal subjects and were positively correlated with serum cortisol, DHEAS and ADS levels, irrespective of corticosteroid treatment. In addition, serum levels of cortisol in relation to IL-6 were significantly lower in patients with chronic disease and long-term corticosteroid administration compared with patients with recent onset PMR and without corticosteroid therapy.

However, serum levels of cortisol in PMR patients with or without corticosteroid were lower than would have been expected considering their inflammatory status (increased IL-6) (10). This may indicate a change in the responsiveness of the HPA axis to inflammatory stimuli such as IL-6 during active disease. As already shown, IL-6 together with ACTH act synergistically to stimulate the direct release of corticosterone from the adrenal gland and this effect might well be implicated in the altered HPA axis responsiveness observed in PMR patients (11). Furthermore, there seems to be a shift of steroid biosynthesis to cortisol in relation to DHEAS or ADS in chronic PMR, as indicated by the higher ratio of serum cortisol/serum DHEAS in patients (particularly those with long-standing disease and prior corticosteroid treatment) compared to normal subjects (10).

As a matter of fact, healthy adrenal glands are capable of secreting the amount of endogenous cortisol necessary to control pathologic conditions under circumstances involving a strong activation of the hypothalamus, including acute stress (i.e., surgery, infections, severe interpersonal stress) (12). However, this does not seem to be the case in PMR patients. Therefore, several factors must be responsible for the alteration of the HPA axis in PMR patients, including chronic systemic inflammatory stimuli (i.e. infections) with elevated IL-6 and TNF serum levels, the age-related decrease in anti-inflammatory hormones such as gonadal and adrenal hormones (i.e., testosterone, DHEA, ADS), corticosteroid therapy, and chronic activation of the defense system against stress (i.e., psychosocial stressors and variables such as coping and personality) (13).

In summary, such factors – which lead to the continuous stimulation of the HPA axis – could result in adaptive changes, i.e. the inadequately low secretion of adrenal and gonadal hormones in relation to systemic inflammation.

Inefficient adrenal hormone production and clinical correlations in PMR patients

In order to evaluate adrenal function in PMR patients, we recently assessed HPA axis activity under basal conditions and then after stimulation with desmopressin (DDAVP) and ACTH (14). Although based on a small sample, the preliminary data show that PMR patients present a similar HPA axis reserve in comparison to healthy subjects. On the contrary, we found increased basal and ACTH-stimulated 17-hydroxyprogesterone levels in PMR patients (14). This could suggest a
 preferential drive of adrenal steroidogenesis towards 17-hydroxyprogesterone, which is the key element for adrenal cortisol production (14). Thus, 17-hydroxyprogesterone and subsequent cortisol production may be stabilized, probably at the expense of the adrenal androgens (10, 14).

In a very recent study, 40 PMR patients were evaluated for serum levels of cortisol, DHEAS and ASD, as well as IL-6 at baseline and then every 3 months for at least a 12-month follow-up period (manuscript in preparation, Salvarani & Cutolo). Laboratory and clinical parameters of the disease [i.e., the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), joint pain localization, stiffness, disease duration, number of relapses etc.] were correlated with the hormonal levels in both sexes. Interestingly, at baseline DHEAS and ASD levels were significantly lower in female patients and higher in male patients, compared to age and sex-matched normal controls. On the contrary, cortisol at baseline was found to be significantly higher only in female PMR patients. This indicates that the HPA axis was more chronically activated and that cortisol secretion was stabilized at the expense of adrenal androgens in female as compared to male patients.

During the 12-month follow-up, positive correlations were observed between cortisol and ESR/CRP in both male and female patients, and between DHEAS/ASD and ESR/CRP in female patients. Furthermore, a negative relationship was shown in female PMR patients between the number of relapses and DHEAS/ASD (14). This study seems to confirm that in PMR a lower than expected production of adrenal steroids is observed, considering the patients’ inflammatory status, particularly in females. Generally, the adrenal steroid levels were found to be negatively correlated with the number of relapses and the duration of corticosteroid therapy. In addition, the duration of corticosteroid treatment was found to be negatively correlated with the laboratory parameters of inflammation over the 12-month study period. After the initiation of corticosteroid therapy, a rapid and stable decrease in IL-6 serum levels within one month was seen together with a normalization of the inflammatory parameters and adrenal hormones.

Serum IL-6 was confirmed to be a sensitive marker of disease activity in PMR (15). Therefore, in PMR patients hormone replacement therapy in the form of corticosteroid administration seems to be necessary in order to overcome adrenal hypofunction.

The adrenal steroid "replacement" therapy in PMR

Among the rheumatic diseases, PMR has been neglected for many years, not the least because of the false impression that its management is "easy" once corticosteroids are started (16, 17). The fact is that spontaneous disease flares may occur independently of the corticosteroid dosage, the amount of corticosteroids administered must be carefully adjusted in relation to disease activity, and therapy has to be maintained for a long period of time (16).

Another peculiar characteristic of PMR is the rapid improvement seen following the initiation of corticosteroid therapy at a dose ranging from about 20 to 30 mg of prednisolone (17). This dosage is equivalent to about 80-120 mg of endogenous adrenal gland-derived cortisol and represents approximately 3 times the daily secretion rate of a healthy adrenal gland (18). Interestingly, during septic shock or in the case of the intravenous administration of cytokines such as TNF or IL-6, the healthy human adrenal gland is capable of secreting up to 300 mg of endogenous cortisol daily (19-21). Hence, the question arises as to whether or not the adrenal glands of elderly patients with PMR are able to produce the amount of cortisol necessary to control inflammation. As we have mentioned above, there is a reduced responsiveness of the HPA axis to inflammatory stimuli in PMR patients. Naturally the age-related decline in adrenal gland function is an important predisposing factor, probably at the moment of disease onset. Changes in steroidogenesis due to the direct effects of cytokines at the level of the adrenal glands during any inflammatory reaction may further augment adrenal insufficiency under the condition of a chronic disease (10) (Fig. 1).

Conclusions

PMR patients demonstrate altered HPA axis functioning at disease onset, prior to corticosteroid treatment, and during the course of the disease. This is indicative of a reduced responsiveness of the HPA axis and reinforces the hypothesis that there are close similarities between PMR and EORA (24). Several factors could be involved in this adrenal hypo-function, such as the concomitant physiological decline in adrenal steroidogenesis during aging, chronic stress system activation, chronic infections (for example, by Chlamydia pneumonia or herpes viruses), altered adrenal hormonal pathways (inter-individual and genetic differences), and age-related changes in gonadal hormone biosynthesis (i.e., estrogens) (Fig. 1).

The abrupt onset of PMR, with symptoms reminiscent of the steroid withdrawal syndrome (i.e., myalgia, malaise, fever, pain, depression, sleepiness, anorexia, etc.) and of adrenal insufficiency, and the dramatic and rapid disappearance of these symptoms following corticosteroid administration, could very well represent further strong clinical evidence that PMR is an HPA-axis driven disease.

References


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