CYP17 polymorphisms and androgen levels in postmenopausal patients with rheumatoid arthritis

Sir,

Recently we read the stimulating article by Huang et al. in which they observed a relationship between CYP17 genotypes and the age at onset of rheumatoid arthritis (RA) in female patients (1). The CYP17 gene, coding for the cytochrome P450c17α, mediates both steroid 17α-hydroxylase and 17,20-lyase activities that represent the key points in human steroidogenesis (Fig. 1). A single base change in the 5′ promoter region of the CYP17 creates an additional Sp-1-type promoter site which might cause increased expression (2). A new recognition site is presented as two alleles (A1 and A2) that the authors investigated in their RA study. Interestingly, Huang et al. found that female RA patients with the A2 allele tended to develop the disease at younger age than those without, and having the A2 allele was a protective factor from older age onset female RA. The results of the study suggest that the A2 allele is related to early onset, and the A1 allele to the late onset. As a matter of fact, the A2 allele, being an expression of increased CYP17 activity, is thought to be linked to elevated production of both estrogens and androgens through increased transcription. By considering that androgens function generally as immunosuppressors, whereas estrogens function as immunostimulants and by assuming that having the A2 allele could modify the onset of RA, the authors suggest that the effects of the androgen increase induced by the A2 presence, might be not biologically influential in the fertile age (younger RA female patients), which is characterized by high estrogens (immunostimulant). However, the same induction of increased production of androgens (immunosuppressive) might become an influential resisting factor in older women, who are characterized by physiologically reduced estrogens (3). The conclusions of the study by Huang et al. induced us to re-evaluate the results of an investigation we published 15 years ago, in which we found statistically higher concentrations of androgens, particularly testosterone (T), androstenedione (A) and dehydroepiandrosterone (DHEAS) in the serum of postmenopausal women affected by RA when compared to age-matched healthy controls (4). Slightly higher T and A were found again in postmenopausal when compared to premenopausal RA patients. On the contrary, T, A and DHEAS levels in premenopausal patients, were not statistically different from their age-matched healthy controls. The results of the study suggested that in postmenopausal RA patients an androgen status similar to that found before menopause persists. At that time, the significance of the unexpected relative hyperandrogenism in postmenopausal patients was not clear. During the following years, other studies showed contrasting results concerning serum androgen levels in postmenopausal RA patients, reporting both significant and non-significant increases of androgens, as well as decreased levels (5-9).

The discussion regarding the contrasting serum androgen levels observed in postmenopausal RA patients by different authors, was partially explained by the different characteristics of the control populations evaluated (healthy subjects in some studies, osteoarthritic patients in other studies) (10). In addition, the use of corticosteroids in some RA populations evaluated within the studies, might have induced altered androgen levels as a consequence of the treatment.

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In the light of the results of Huang et al. whenever confirmed, new possible explanations for the observed increase of androgen levels in postmenopausal RA patients, are now arising and might clarify the previous unexpected results (4). Therefore, if we consider that androgens are implicated in the pathogenesis of RA as natural immunosuppressors, and that male RA patients are characterized by low serum androgens, the increased androgen levels, as expected in the A2-allele positive female patients, may play effectively a protective role, as suggested by Huang (11, 12).

The feasible different distribution of the A2 allele positivity in different populations, may explain the contrasting serum androgen levels observed in the various reported RA studies, in relation to the postmenopausal status. Of course, androgen levels represent only one of the factors involved in the pathogenesis of RA, other factors include genetic components, the stress system response and infective agents (13). In conclusion, the relation-

\[ \text{Cholesterol} \]
\[ \text{P 450} \text{SCC (Cholesterol side chain cleavage enzyme)} \]
\[ \text{Pregnenolone} \]
\[ \text{P450 } \alpha \ (17\alpha \text{-hydroxylase)} \]
\[ 17\text{-Hydroxyprogrenolone} \]
\[ \text{Progestrone} \]
\[ \text{P450 } \alpha \ (17\beta \text{-hydroxylase)} \]
\[ 17\text{-Hydroxyprogesterone} \]
\[ 3\beta\text{-HSD (hydroxysteroid dehydrogenase/soromere)} \]
\[ \text{Dehydroepiandrosterone} \]
\[ \text{Androstenedione} \]
\[ \text{Testosterone} \]
\[ \text{17\beta\text{-HSDOR (17\beta\text{-hydroxysteroid oxidoreductase)} \]
\[ \text{17\beta\text{-HSDOR (17\alpha\text{-hydroxysteroid oxidoreductase)} \]
\[ \text{Estrone} \]
\[ \text{Estradiol} \]

Fig. 1. Key enzymes involved in steroidogenesis. The CYP17 gene, coding for the cytochrome P450c17α, mediates both steroid 17α-hydroxylase and 17,20-lyase activities. Increased transcription of these enzymes (presence of allele A2) might determine the increased synthesis of androgens (androstenedione, dehydroepiandrosterone and testosterone).
ship between the CYP17 gene polymorphism and RA should be tested by further investigations of serum androgen levels.

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References

Reply
Sirs.
Serum hormone measurements are subject to variation by many factors such as time of day, age, disease status, and prescribed medication, whereas the determination of genetic markers for steroidogenesis is not influenced by such variance.
We have demonstrated that the CYP17 gene polymorphism is associated with RA, especially in older age onset female RA, through sex hormone production (1). Parallel with our results, with a large sample using sibpair analysis methods, John et al. reported that the estrogen synthase (CYP19) locus was linked to RA and that this linkage was strongest in patients with onset at over 50 years old, when serum hormone levels decline (2). The functional activities of the CYP19 gene variants are unknown at the present. Furthermore, though both CYP17 and CYP19 are related to sex hormone synthesis, their genes are located in different chromosomes.
We have also demonstrated an association between both androgen and estrogen receptor gene polymorphisms and RA onset (3, 4). Shorter CAG repeats of the androgen receptor gene, presenting high levels of transactivation activity, are related to younger age onset male RA when serum androgen levels are higher (3). In addition, some intron variants of the estrogen receptor gene are related to the onset of female RA at a certain age period, probably depending on the serum levels of estrogens (4). Overall, the results of our studies possibly explain the hypothesis of Cutolo et al., which states that sex hormones, especially androgens, play an important role in the pathogenesis of RA.

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Letters to the Editor

Sirs.
We read the article by Amit et al. “Headache in systemic lupus erythematosus and its relation to other disease manifestations” in the July - August issue of the Journal (1) and found it of great interest. The authors described a large series of SLE patients with headache, which appears as a frequent symptom, and found a correlation to constitutional and musculoskeletal manifestations.
We would like to emphasize and highlight a rare but severe form of headache in SLE. We previously reported (2) on 3 girls with SLE who developed cerebral vein thrombosis (CVT). In one of them the diagnosis was delayed until severe hemorrhagic infarct occurred. The clue to the diagnosis in the 3 patients was severe, persistent, throbbing, unremitting headache, unresponsive to daily analgesic drugs. All 3 showed the presence of antiphospholipids antibodies. Radiological studies, CT, MRI, and MR venography confirmed the CVT. As Amit et al. concluded, headache in SLE is common, but rarely a higher index of suspicion for the unusual “lupus headache”, should lead to intense investigations enabling early diagnosis and treatment.

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References