HLA Antigens in Methotrexate-induced Liver Cirrhosis

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Abstract. HLA typing was carried out in 20 psoriatics with methotrexate-induced liver cirrhosis and 44 methotrexate-treated psoriatics who at the time of investigation had not developed cirrhosis. The data were compared with results from tissue typing of 1291 healthy individuals. The antigen combination A1, B8 was found to be increased among patients with cirrhosis vis-à-vis methotrexate-treated psoriatics who did not develop liver cirrhosis. This finding is similar to data on chronic active hepatitis type A and drug-associated chronic active hepatitis. Findings of the antigen combination A1, B8 should—just as with other predisposing factors—lead to caution in liver control in psoriatics on methotrexate therapy.

Key words: HLA antigens; A1+B8; Methotrexate; Liver cirrhosis

Liver cirrhosis in methotrexate-treated psoriatics has been on record since 1968 (1, 2). Data from an international cooperative study (9) as well as from individual studies (6, 10) have indicated that liver damage in methotrexate-treated psoriatics can often be related to multiple factors acting on the liver during methotrexate therapy, such as alcohol intake, age, diabetes, obesity, previous intake of arsenic and maybe psoriasis itself. The present study demonstrates an association with histocompatibility antigens.

MATERIAL AND METHODS

The diagnosis of cirrhosis was established histologically in 20 of 183 methotrexate-treated psoriatics (11) all of whom were monitored with liver biopsies taken at average intervals of 1 year. HLA typing was performed by the method of Kissmeyer-Nielsen & Kjerbye (3) in all patients with cirrhosis and the results compared with data from HLA typing of 44 methotrexate-treated psoriatics, who at that time had not developed signs of liver cirrhosis. The two groups of patients were comparable in respect to sex, age and cumulative dosage of methotrexate. The average cumulative dosage in patients with cirrhosis was 2400 mg, in control patients 2200 mg methotrexate. Another control group consisted of 1291 healthy individuals. For statistical evaluation the χ-square test was used. This study did not include data on C and D loci.

RESULTS

Table 1 shows the frequency of HLA-A1, HLA-B8 and the A1+B8 antigens in methotrexate-treated psoriatics with and without cirrhosis, in the combined group, as well as in healthy controls. The HLA types of psoriatics did not differ as a whole from findings of our earlier studies on psoriasis (8) and, as can be seen from the table, the patient group did not differ from non-psoriatic controls in relation to the above-mentioned tissue antigens.

Although the frequency of HLA-B8 was approximately the same within all groups and the HLA-A1 level was only insignificantly increased in cirrhosis patients, the antigen combination of A1 and B8 was found to be increased among patients with cirrhosis compared with methotrexate-treated psoriatics who did not develop cirrhosis. The p-value was <0.05 and as this confirms other studies of drug-induced chronic active hepatitis it can be considered significant. The antigen combination was represented in 5 of 20 patients.

DISCUSSION

HLA studies in liver diseases include studies on chronic active hepatitis (CAH) also drug-associated CAH. Five studies on CAH type A (5) have been consistent in showing increased frequencies of

Table 1. *Frequencies (per cent) of HLA-A1 and HLA-B8 antigens in methotrexate-induced liver cirrhosis*

Antigens	MTX-treated with cirrhosis (n=20)	MTX-treated without cirrhosis (n=44)	All patients (n=64)	Controls (n=1291)
HLA-A1	45.0	27.3	32.8	32.0
HLA-B8	25.0	18.2	20.3	23.6
HLA-A1+B8	25.0	6.8	12.5	15.2

For statistical evaluation, the χ-square test was used.

HLA-A1 and B8, and in one of the studies (7) the A1, B8 haplotype was represented in 8 out of 13 cases with B8. In a study on 13 cases of drug-associated CAH, there was an increase in HLA-A1 and B8 (4). In alcoholic cirrhosis an insignificant excess of HLA-B8 has been reported (5). Other associations of HLA antigens have been found in other types of liver disease. Typing of D-locus antigens in chronic active liver disease has shown a significant increase in DW3 (5) and this association may be of greater importance than the findings within the A and B loci. As mentioned, we have not typed for D locus. Our studies nevertheless support the idea of a genetic predisposition for methotrexate-induced liver cirrhosis and suggest a common factor for this multifactorial condition with the above-mentioned liver disease.

The finding of the A1 and B8 should—just as with other predisposing factors—lead to extra caution in liver control in a psoriatic undergoing methotrexate treatment and, if found prior to treatment, be included in the relative contra-indications to this drug.

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The Effect of Zinc on the Sebum Secretion Rate

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Abstract. In accordance with a randomized double-blind experimental design, capsules of zinc sulfate, 440 mg total daily dose, and lactose placebo were administered orally to 10 normal Caucasian males for 3 weeks. Sebum secretion rates and serum zinc levels were determined prior to and following treatment. There was a statistically significant change in the before and after mean sebum secretion rates of the zinc group when compared with those of the placebo group ($p<0.028$). The results of this preliminary study indicate that supplemental zinc sulfate may reduce the quantity of skin-surface sebum. Further investigation is warranted.

Key words: Zinc; Sebum Secretion Rate

The essential trace metal zinc has been linked to numerous biological processes in man. It plays a role in at least twenty enzyme systems (7), helps to stabilize macromolecules and biological membranes and influences the phagocytic activity of macrophages (3).

There are conflicting reports in the literature regarding the value of oral zinc therapy in acne vulgaris. A recent report concluded that zinc "has no early clinical effect on male patients with moderate acne". (6) In contrast, Michaëlsson et al. (5) and Hillström et al. (4) suggest that acne improves significantly following zinc sulfate therapy. Interestingly, Michaëlsson noted that the skin of some patients who received zinc sulfate became dryer and