# The Levels of Complements and the Frequency of Class II Major Histocompatibility Complex Antigens in Patients with Autoimmun Chronic Liver Disease

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***Özet:*** *OTOİMMÜN KRONİK KARACİĞER HASTALIKLARINDA HLA-DRW DOKU GRUBLARININ DAĞILMI VE KOMPLEMAN DÜZEYLERİ*

*Otoimmun hastalıklarla, histokompatibilite antijenlerinin ilişkisi bilinen bir gerçektir. Son zamanlarda PBS, PSK, ve OKAH de farklı HLA-Class II antijenlerle beraberliğini tanımlayan çalışmalar yayınlanmıştır. Bu çalışmada da primer bilier siroz (PBS), primer sklerozan kolanjit (PSK) ve otoimmun kronik aktif hepatit (OKAH)'li olgularda HLA-Cass II antijenlerinin beraberliği ve serum kompleman C4 düzeyleri araştırılmıştır. Çalışmada 6 PBS, 2PSK, 2OKAH olgusu yer almıştır. Sonuçta otoimmun kronik karaciğer hastalıklarında relatif riski belirleyen, istatiksel olarak anlamlı bir histokompatibilite antijeni belirlenememiştir fakat 8 olguda HLA-DRw 52 antijeni splitleri belirlenmiştir ki bu bulgu anlamlıdır ve çalışmanın devamı planlanmıştır.*

**Anahtar kelimeler:** PBS, PSK, OKAH, histokompatibilite antijenleri (HLA – Class II).

***Summary:*** *It has been known that there might be an association between the development of chronic autoimmun liver diseases and their immunogenetic background. Recently many studies revealed that an high frequency of HLA-DRw8 was related to autoimmune liver disease(ALD) such as Primary Biliary Cirrhosis (PBC), Primary Sclerozan Cholangitis (PSC) and autoimmun chronic hepatitis (ACH). Particularly it has been shown that HLA-DRw52 and HLA-DR8 are high of incidance in patients with PSC.*

*We studied major histocompatibility complex antijens by microtoxicity and serum complement levels, C4-C3, by Radioimmunassay(RAI). In ten patients with ALD, six had PBC, 2 PSC, 2 had ACH, and in 112 patients control group.*

*In this study, the split of HLA-DRw58 has been found to be positive in 8 of the ten patients, which can signify a relative risk of the diseases. This a preliminary report and in order to reach a clear cut conclusion, larger patients group is needed to study.*

**Key words:** PBC, PSC, ACH, histocopatibility antigens. (HLA-Class II).

Immunologic and genetic factors have been accused in the pathogenesis of PSC, PBC and ACH as circulating auto antibodies, polyclonal hypergammaglobulinemia, tissue damage related to T lenfocyte toxicity, the presence of the other autoimmune diseases and the predilection involvement for female patients are the main characteristics of the disease(1,2). Particularly in the pathogenesis of PSC, a defect in cell mediated immunity has been strongly suggested(3). A group of cell membrane antigens has been playing an important role in the regulation of the immune system function. These antigens were coded by the genes of major histocompatibility complexes which are located at short arm of sixth chromosome. It is possible to divide HLA into three subgroup according to their structures and molecular weight;

HLA-Class I; HLA-A,B,C.

HLA-Class II; HLA-DR, DQ, DP.

HLA- Class III; Protein of complements

The gene of MhC is very important in determining the association of the disease with HLA. It is

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**Table I:** Typing of HLA-Class II in 10 patients with autoimmun discane.

| Patients | HLA-DR | HLA-DQ |
|---|---|---|
| 1- V.O | DRw15 (2, Qw1) | DQw6 (Qw1) |
| | DR4 (w53,Qw3) | DQw7 (Qw3) |
| 2- N.G | DRw13 (6,w52,QW) | DQw6 (Qw1) |
| 3- S.T | DR4 (W53, QW3) | DQw7 (Qw3) |
| | DRw13 (6,w52, Qw) | DQw5 (QW1) |
| 4- Y.Y | DRw17 (6,w52, QW) | DQw2 |
| 5- M.H | DR4 (w53. Qw3) | DQw7 (Qw3) |
| 6- E.H | DRw11 (5,w52, Qw) | DQw7 (QW3) |
| 7- Z.B | DRw11 (5,w52, Qw) | DQw7 (Qw3) |
| | DRw8 (w52, QW3) | |
| 8- S.O | DRw15 (2, Qw1) | DQw7 (Qw3) |
| | DRw8 (w52, Qw3) | DQW6 (Qw1) |

**Table II:** The levels of C3-C4 in 10 patients with autoimmun liver disease.

| Patients | Activation of disease | C3 (N:50-120 mg/dl) | C4 (N:20-50 mg/dl) |
|---|---|---|---|
| (1) | Active | 52,9 | 5 |
| (2) | - | 174 | 56 |
| (3) | Active | 148 | 58 |
| (4) | - | 53 | 13 |
| (5) | - | 125 | 54 |
| (6) | - | 158 | 34 |
| (7) | - | 125 | 34 |
| (8) | - | 139 | 47 |
| (9) | - | 144 | 32 |
| (10) | Active | 82 | 9 |

known that some. HLA provide a predisposition for the development of some kind of diseases. This association is particularly clear in HLA-Class II antigen. There is no clear-cut consensus on immunogenetic status of autoimmun liver diseases(1).

In this preliminary study, our aims were to determine histocompatibility antigens, in patients with ALD and to compare with control group antigens and with the literature.

## MATERIAL and METHODS

There were 10 female patients with auto immune liver disease(6 with PBS, 2 with PSC and 2 with ACH). The mean age was 35.6 ranged from 30 to 56 years old. Diagnosis of the disease was based on clinical data, liver function tests, auto antibodies including AMA-ASMA-ANA and anti DNA antibodies, immun globulin levels, ERCP and liver biopsy.

Major histocompalibility antigenes, HLA-Class II were determined by micro toxicity and the levels, by complements, C3, C4, were measured by RIA. The same tests were done in 122 patients control group.

**Table III:** The Distrubition of HLA locus and the results of $x^2$ test in determining of relative risk of both groups.

| HLA Lokus | Patients n-10 % | | Control groups n-112 % | | p değeri | RR |
|---|---|---|---|---|---|---|
| DRw15 | 2 | 20 | 23 | 20,5 | p>0,05 | 0,97 |
| DR4 | 3 | 30 | 24 | 21,4 | p>0,05 | 1.40 |
| DRw13 | 2 | 20 | 22 | 19,6 | p>0,05 | 1.02 |
| DRw17 | 3 | 30 | 21 | 18,7 | p>0,05 | 1.60 |
| DRw11 | 3 | 30 | 36 | 32,1 | p>0,05 | 0.93 |
| DRw8 | 1 | 10 | 5 | 4,4 | p>0,05 | 2.24 |
| DQw1 | 4 | 40 | 60 | 53,5 | p>0,05 | 0.75 |
| DQw2 | 3 | 30 | 34 | 30,3 | p>0,05 | 0.99 |
| DQw7(3) | 6 | 60 | 58 | 51,7 | p>0,05 | 1.16 |

## RESULTS

Table I and II shows the results of HLA-Class Ii and complement levels respectively. Table III reveals the comparison of the study group results with the control group results. In 8 of the 10 patients, the splits of HLA-DRw52, which are HLA-DRw17 and HLA-DRw8, have been found to be positive, which is relatively significant when compared with those of control group. The frequency of the antigens investigated has not been found significant statistically (P>0.05), by using x2 test for comparison of the results of study group with control group. The levels of C4 was decreased only in 3 cases (30%).

## DISCUSSION

Immunogenetic bases of PBS has not been investigated until recent years. In a couple of study from Spain (4) and from USA (5), The association of HLA-DR3 and HLADRw8 with PBS has been found significant. It is a new option that the low levels of C4 and the presence of appro-

**Table IV:** The Distrubition of HLA-Class II antigenes of patients with PBC, aCAH, PSC ( in the literature).

| PBS | aCAH | PSC |
|---|---|---|
| HLA-DRw8(36%) | HLA-B8(48%) | HLA-B8 (50%) |
| HLA-DR3 | HLA-DR3(53%) | HLA-DRw52a(35%) |
| | HLA-DRw52/ANA (+)(31 %) | |
| | HLA-DR4/ANA(+) (16%) | |

priate HLA-Class II antigens can predict the relative risk of PBC. The role of auto immune factors has been understood by demonstrating of anti-neutrophiles antibodies(3), consequently this disorder has been considered as a auto immune liver disease. There are many similarity between PSC and PBS in term of prognosis and the treatment, thus predictability of PSC by testing of HLA-Class II can be possible (1,8,9,10). The association of some antigens such as HLA-DR52a which is a member of HLA-Class II with PSC is quite interesting and worthy for investigation (7,11).

The presence of HLA-DR3 and HLA-B8 in ACH (6,12) can be important in predicting of the occurrence of the disease. In this study, the splits of HLA-DR52, HLA-DR12 and HLA-DRw8 have been found to be relatively significant. Considering HLA-DRw8 its presence has not been estimated significant in risking of the disease(RR; 2.24 and $p>0.05$). Since patients group was so small, it is quite difficult to reach any conclusion.

The level of C4 were lowe in only 3 cases. In 2 of the 3 patients, the disease was in active period. It can be said that C4 levels is a marker in the assesement of the disease activity. We have been keeping on studying about this matter. As long as the number of cases increas. It will be able to reach a suggestion.

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