HLA-A24: RISK FACTOR IN PROLIFERANTE DIABETIC RETINOPATHY

HLA-A24: FACTOR DE RIESGO EN RETINOPATÍA DIABÉTICA PROLIFERANTE

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ABSTRACT

Objective: Proliferative diabetic retinopathy (PDR) is characterized by a progressive visual impairment in young people. Human leucocyte antigen (HLA)-A24 is a well-established factor associated with the pancreatic islets of Langerhans lost in this process. Our aim was to study further the relationship of the HLA-A24 associated with PDR.

Materials and methods: We evaluated a group of patients with PDR (n=95) and a healthy control group (n=60). HLA-A24 for each participant in the study was determined by molecular hybridization techniques.

Results: The control group showed a lower frequency of HLA-A24 compared with the PDR group (p = 0.043). HLA-A24 was associated with PDR (OR = 5.4; 95% CI= 3.2-7.6; p< 0.001).

Conclusions: HLA-A24 is not a protective factor for PDR, but is a risk factor of its development (Arch Soc Esp Oftalmol 2007; 82: 753-756).

Key words: Insulin-dependent diabetes, proliferative diabetic retinopathy, HLA, HLA-A24, risk factor.

RESUMEN

Objetivo: La retinopatía diabética proliferante (RDP) se caracteriza por pérdida de la visión en la población joven. Está bien establecido que el antígeno leucocitario humano (HLA)-A24 es un factor de riesgo para la pérdida total de las células del páncreas. Nuestro objetivo es estudiar la asociación del HLA-A24 con la RDP.

Material y método: Se estudió un grupo de pacientes con RDP (n= 95) y un grupo control (n= 60). A todos se les determinó el HLA-A24 mediante técnicas hibridación molecular.

Resultados: El grupo control mostró menos frecuencia de HLA-A24 que el grupo con RDP (p= 0,043). El HLA-A24 se asoció a retinopatía diabética proliferante (OR = 5,4; 95% CI= 3,2-7,6; p< 0,001).

Conclusiones: El HLA-A24 no es un factor de protección para la retinopatía diabética proliferante, es un factor de riesgo para desarrollarla.

Palabras clave: Diabetes insulíndependiente, retinopatía diabética proliferante, HLA, HLA-A24, factor de riesgo.
INTRODUCTION

The evolution time of diabetes and chronic hyperglycemia are the best known and established risk factors for the development of diabetic retinopathy. However, there is a group of patients who, in spite of inadequate glycemia controls, do not develop diabetic retinopathy whereas other patients with a strict control develop severe forms of retinopathy which will even resist different therapies (1,2). The human leucocyte antigen system (HLA) plays an important role in the response and tolerance of the immune system and, in diabetes type one patients, retinopathy has been related with antigens in the DQ region (3). Some authors (4,5) have described a strong relationship between the presence of HLA-A24 and the complete destruction of beta cells in the pancreatic islets in insulin-dependent diabetes patients. Therefore, it can be speculated that these patients will develop retinopathy earlier and will progress in a more aggressive manner than in HLA-A24 negative insulin-dependent diabetes patients. On the basis of this premise, this study was planned with the objective of establishing the relationship between HLA-A24 and diabetic retinopathy in its severest forms in a sample of patients.

SUBJECTS, MATERIAL AND METHODS

This study was approved by the Research and Teaching Committee of our hospital. The patients were recruited from the Retina and General consulting rooms. 95 insulin-dependent diabetes patients were studied between 1998 and 2005. The inclusion criteria for the patients were as follows:

— Acceptance of participation in the study with signature of an informed consent document.
— Insulin-dependent diabetes mellitus treated by endocrinologist, in turn or primary health care practitioners, with ten or more years of revolution.
— Diagnostic of severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy (PDR).
— Access to their medical records.

An eye fundus study under midriasis was performed by the same ophthalmologist who classified the results for this study as severe nonproliferative diabetic retinopathy or proliferative retinopathy (PDR) (n= 95). The control group was made up by sixty healthy relatives.

In each case an HLA-A24 screening was performed with molecular hybridation in total blood (PCR/SSO). The association between HLA-A24 and PDR was calculated by pondering the odds ratio (OR) and its corresponding confidence interval to a confidence of 95%. The analysis, based on gender and age, was made through logistic regression.

RESULTS

Table I shows the characteristics of the study population, without statistically significant differences between cases and controls. Table II shows the degree of significance of HLA-A24 in patients vis-à-vis the control group and the results of the odds ratio calculation of this HLA between the group of patients and the control group. The HLA-A24 dependent risk indicates that the probability of PDR increases in a factor of 5 (IC 95%= 3.4-8.3; p<0.001). The control group exhibits a lower frequency of HLA-A24 (11%) compared with the group of patients (55%) (p= 0.043). The Association of HLA-A24 is significant in all age groups:

- 30-40 years: OR= 11.2; CI 95%= 4.76-24.80
- 40-50 years: OR= 7.26; CI 95%= 3.4-19.80
- 50-60 years: OR= 10.2; CI 95%= 4.87-21.70
- 60-70 years: OR= 11.6; CI 95%= 4.66-23.40
- 70-80 years: OR= 7.23; CI 95%= 3.45-18.76
- 80-90 years: OR= 5.26; CI 95%= 2.67-10.21

HLA-A24 is associated to PDR in a similar way in men (OR= 5.1; CI 95%= 2.57-10.21) and in women (OR= 5.31; CI 95%= 2.87-11.34).

<table>
<thead>
<tr>
<th>PDR</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>Nr.</td>
<td>95</td>
</tr>
<tr>
<td>Gender</td>
<td>63.16% women</td>
</tr>
<tr>
<td>Age</td>
<td>66.5 SD 5.8</td>
</tr>
<tr>
<td>Age of diagnostic</td>
<td>43.9 SD 7.6 años</td>
</tr>
</tbody>
</table>

PDR: proliferative diabetic retinopathy/severe nonproliferative diabetic retinopathy; Nr.: number.

Table II. HLA-A24 and degree of association with PDR against controls

<table>
<thead>
<tr>
<th>% of HLA-A24</th>
<th>OR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDR</td>
<td>55%</td>
<td>5.4</td>
</tr>
<tr>
<td>Control</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

HLA: Human Leucocyte Antigen; OR: odds ratio; CI: confidence interval; PDR: proliferative diabetic retinopathy/severe nonproliferative diabetic retinopathy.
DISCUSSION

It has been clearly established that strict control of glycemia is the best tool for preventing diabetic retinopathy (1). However, there is a group of diabetic patients who will develop diabetic retinopathy in spite of adequate controls, whereas others will not develop it in spite of a poor control. This may indicate that the risk factors for diabetes and retinopathy need not be the same and that genetic factors may influence the susceptibility of developing severe retinopathy (2).

Diabetes type one is caused by a failure in the self immune system and is associated to specific HLA (3). HLA is very interesting due to the numerous implications it has in biology and medicine, but perhaps its most remarkable characteristic of this antigen system is the influence it has on the susceptibility to a high number of diseases (6).

The influence of genetic factors in the development of diabetic retinopathy has not been studied with great interest because, until recently, it was considered to be unrelated to ophthalmology and because HLA studies are expensive and the labs do not have the technology for the less frequent types such as HLA-A24. In insulin-dependent diabetics, the number of residual cell islets influences the quality of glycemia control and the complete destruction of Langerhans islets is related to the presence of HLA-A24 (4,5).

Some studies refer to the influence of HLA as a genetic marker for diabetic retinopathy (7,8) considering the HLA system as the biggest risk factor for the development of proliferative diabetic retinopathy regardless of glycemia levels.

This paper aims at analyzing the relationship between HLA-A24 and PDR in a group of patients and a control group. As the latter is formed by relatives of PDR patients, the effect of environmental and economic factors which may influence the development of diabetes is minimized. Accordingly, it is recommendable to study groups with the highest possible homogeneity. In our population the relationship between HLA-A24 and PDR is confirmed and the presence thereof increased five times the risk of suffering it. The association between HLA-A24 and the total destruction of pancreatic islets (4,5) signifies a total lack of insulin with faulty glycemia control the twenty four hours of the day, exhibiting an exaggerated hyperglycemia followed by intense hypoglycemia, leading to a total loss of vascular self-regulation.

The patients of Nakanishi K et al. (10) with complete destruction of cells exhibited an early evolution to severe forms of diabetic retinopathy and 89.6% of patients had HLA-A24. In a study with insulin-dependent diabetic families, Honeyman MC et al (11) considered that HLA predisposes to diabetes and influenced its progression. Mimura T et al (12) established that several types of HLA I and HLA II indicated the prognosis of retinopathy in patients with diabetes type one. In conclusion, our work shows that HLA-A24 is a risk factor for developing the most severe forms of diabetic retinopathy. Even so, we do not recommend the systematic study of HLA-A24 as a diagnostic test, but we consider it important to establish intervention groups with preventive measures from the beginning.

REFERENCES
