FAMILIAL ASSOCIATION IN AUTOIMMUNE LIVER DISEASE

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Abstract

The occurrence of autoimmune liver disease in members of the same family is hardly a frequent observation in clinical practice. In a group of 204 cases of primary biliary cirrhosis (PBC) (196 women) and 219 of type 1 autoimmune hepatitis (AIH) (183 women), seen from 1985 to 2000, family occurrence of autoimmune liver disease was investigated. Diagnosis of both entities was based on clinical criteria, immunological studies and liver biopsy. Six families were identified with 2 members each presenting with autoimmune liver disease. In 4 of them the index case had an AIH. This association was observed between mother and daughter in 3 instances. In the remaining AIH index case the association found was with a PBC in her sister. In the other two families the index cases were PBC. In one of them, PBC and AIH association were observed in sisters. Lastly, in another case, an antimitochondrial (AMA) negative variant of PBC was detected in mother and her daughter. The low frequency of family association observed in this cohort could be due to the fact that only symptomatic cases were included. Concurrent autoimmune manifestations were confirmed in 5 members of 6 families (42%). Our results, given the concurrence of both liver diseases in the same family, suggest a link among diverse entities of the autoimmune lineage. The frequency of AIH family association seems to be more prominent in this series than that of PBC. It is also shown that family association in the case of an AMA-negative variant of PBC is feasible, thus confirming that no substantial differences exist between the latter and AMA-positive PBC.

Key words: primary biliary cirrhosis, autoimmune hepatitis, familial autoimmune liver disease.

Resumen

Asociación familiar en la enfermedad hepática autoinmune. El hallazgo de enfermedades hepáticas autoinmunes en miembros de una misma familia constituye una observación poco frecuente en la práctica clínica. Se estudió un grupo de 204 casos con cirrosis biliar primaria (CBP) (196 mujeres) y 219 con hepatitis autoinmune (HA) tipo 1 (183 mujeres), asistidos entre los años 1985 y 2000. El diagnóstico de ambas entidades se estableció en base a criterios clínicos, inmunológicos e histológicos. La asociación de enfermedad hepática autoinmune fue hallada en 2 miembros de cada una de las 6 diferentes familias. En 4 de ellas el caso índice presentaba una HA observándose en 3 la misma enfermedad en las madres y sus respectivas hijas, mientras que en la restante se comprobó la asociación con una CBP en la hermana. En las otras 2 familias los casos índices tenían una CBP. Una de ellas con la variante anticuerpo antimitocondrial (AMT) negativo presentando la misma variante la madre. En el otro caso, la asociación se observó con una HA en la hermana. La baja asociación observada podría deberse a que solamente se consideraron los casos familiares de enfermedad hepática autoinmune sintomática. El compromiso autoinmune extrahepático se detectó en 5 pacientes de las 6 familias estudiadas (42%). La simultaneidad de la presentación familiar de estas enfermedades con otras manifestaciones extrahepáticas de tipo autoinmune sugieren un mecanismo patogénico común. La asociación familiar en la variante CBP AMT negativa es posible, lo cual confirmaría la ausencia de diferencias entre esta última y la CBP AMT positiva.

Palabras clave: cirrosis biliar primaria, hepatitis autoinmune, enfermedad hepática familiar autoinmune.

Autoimmune liver disease rarely affects different members of the same family. In primary biliary cirrhosis (PBC), however, the same disease seems to occur in family members more frequently than it does in autoimmune hepatitis (AIH). The estimated prevalence of family members with PBC ranges from 1.5 up to 14.9%1-3, but evidence of an immunological disorder in asymptomatic relatives of PBC patients is much greater4. Susceptibility to the disease in relatives of patients with AIH is much less frequent5, although both diseases are thought to be immune-mediated. Because of lack of publications on familiar occurrence in autoimmune liver diseases in Argentina and very few in the rest of the world, we decided to perform the present analysis of the frequency of this type of diseases in family members of patients with PBC and AIH.
Material and Methods

From 1985 to 2000, 204 cases of PBC (female 196, male 8) and 219 (female 183, male 36) cases of AIH type 1 were followed in our Liver Unit.

The diagnostic criteria for PBC were: circulating antimitochondrial antibodies (AMA) by indirect immunofluorescence with titers equal or higher than 1:80, evidence of biochemical or clinical cholestasis and histology compatible with this diagnosis using Scheuer’s classification. The presence of at least 2 out of these 3 criteria was considered necessary to establish the diagnosis of PBC. Thus, diagnosis of AMA negative PBC was established for the presence of biochemical or clinical cholestasis and compatible histology of PBC.

Scheuer’s classification recognizes four histological stages: stage I, florid duct lesion; stage II, ductular proliferation; stage III, scarring and stage IV, cirrhosis.

Exclusion criteria based on ultrasonography, computed tomography, or cholangiography, were extrahepatic bile duct obstruction and features suggestive of other liver diseases.

For AIH type 1 diagnostic criteria were: the presence of antinuclear antibody (ANA) and/or anti-smooth antibody (ASMA) by indirect immunofluorescence with titers equal or higher than 1:80, elevated aminotransferase levels, hypergammaglobulinemia above 2 g%, negativity of viral hepatitis A, B or C markers, exclusion of other causes of liver diseases, good response to immunosuppressive therapy and histology showing a chronic necroinflammatory infiltrate with variable degrees of interface necrosis and fibrosis with or without cirrhosis.

Only those family members of patients with PBC or AIH with overt clinical or biochemical manifestations of any autoimmune liver disease were evaluated.

In all patients, search for other concurrent autoimmune diseases was carried out.

Results

In 423 patients with diagnosis of autoimmune liver disease composed by PBC and AIH, only 12 (2.8%) cases of family association of one of these diseases were detected. This association was observed in 6 families and only in females.

En 4 families, the index case was an AIH showing in 3 of them an association with the same disease between mothers and daughters. In the other AIH the association was present with a PBC in her sister. In the other 2 families the index cases were carriers of a PBC. One of them was AMA positive and the other presented as an AMA negative variant. In AMA positive PBC the association was observed with AIH in her sister. In the other, with AMA negative variant of PBC, the daughter showed the same disease. Extrahepatic autoimmune manifestations were confirmed in 5 members of the 6 families (42%). Familial association as well as concurrent autoimmune manifestation are described in Table 1.

Histologic findings at the moment of diagnosis are shown in Table 2. In the PBC cohort in one case liver biopsy showed slight inflammatory perportal reaction and biliary epithelium damage corresponding to PBC stage I. In 2 cases biopsy revealed epithelial cell damage in small bile ducts, ductular proliferation and portal tract inflammation with lymphocyte extension into perportal parenchyma and a mild fibrosis. These features were considered to be characteristic of stage II PBC. Finally, one case showed advanced fibrosis with moderate inflammatory infiltrate and damage of the biliary duct epithelium, corresponding to PBC stage III.

From the 8 AIH patients, 4 showed an active cirrhosis with interface necrosis, lobular involvement and bridging necrosis and in 4 cases severe chronic hepatitis with rosette formation and moderate fibrosis.

Discussion

The first case of familial PBC was published in 1973; since then not more than some 50 cases have been communicated to date. The great variability in prevalence observed in several studies on familial association in patients with PBC or AIH may be due to the diverse screening methodologies employed. The higher prevalence observed in some studies may be related to

### TABLE 1.– Familial association and concurrent autoimmune manifestation

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age at diagnosis</th>
<th>Index case</th>
<th>Concurrent autoimmune manifestation</th>
<th>Family members</th>
<th>Age at diagnosis</th>
<th>Disease</th>
<th>Concurrent autoimmune manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>57</td>
<td>AIH</td>
<td>ND (mother)</td>
<td>39</td>
<td>AIH</td>
<td></td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>AF</td>
<td>51</td>
<td>AIH</td>
<td>Hashimoto’s thyroiditis</td>
<td>NB (daughter)</td>
<td>41</td>
<td>AIH</td>
<td>Glomerulonefritis</td>
</tr>
<tr>
<td>NM</td>
<td>59</td>
<td>AIH</td>
<td>Sjögren</td>
<td>SM (daughter)</td>
<td>30</td>
<td>AIH</td>
<td></td>
</tr>
<tr>
<td>SL</td>
<td>72</td>
<td>AIH</td>
<td></td>
<td>ML (sister)</td>
<td>69</td>
<td>PBC</td>
<td></td>
</tr>
<tr>
<td>CB</td>
<td>33</td>
<td>PBC</td>
<td></td>
<td>MR (mother)</td>
<td>57</td>
<td>PBC</td>
<td></td>
</tr>
<tr>
<td>MC</td>
<td>44</td>
<td>PBC</td>
<td>EC (sister)</td>
<td>43</td>
<td>AIH</td>
<td></td>
<td>Lupus erythematosus</td>
</tr>
</tbody>
</table>
TABLE 2.– Histologic stage at the time of diagnosis

<table>
<thead>
<tr>
<th>Index case</th>
<th>Patients</th>
<th>Histology</th>
<th>Family members</th>
<th>Patients</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td></td>
<td>AIH with cirrhosis</td>
<td>ND</td>
<td>AIH without cirrhosis</td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td></td>
<td>AIH with cirrhosis</td>
<td>N</td>
<td>AIH with cirrhosis</td>
<td></td>
</tr>
<tr>
<td>NM</td>
<td></td>
<td>AIH without cirrhosis</td>
<td>S</td>
<td>AIH without cirrhosis</td>
<td></td>
</tr>
<tr>
<td>SL</td>
<td></td>
<td>AIH without cirrhosis</td>
<td>M</td>
<td>PBC stage II</td>
<td></td>
</tr>
<tr>
<td>CB</td>
<td></td>
<td>PBC stage I</td>
<td>R</td>
<td>PBC stage III</td>
<td></td>
</tr>
<tr>
<td>MC</td>
<td></td>
<td>PBC stage II</td>
<td>E</td>
<td>AIH with cirrhosis</td>
<td></td>
</tr>
</tbody>
</table>

a greater awareness of the disease and thus most frequent screening in such populations. In this study, we were not searching routinely for the presence for immunologic abnormalities or evidence of cholestasis in all relatives of our PBC or AIH patients, thus only those with overt signs or symptoms of the disease were detected. This means that the true familial association in our series was most likely underestimated.

Environmental factors have also been mentioned as possible causes of a significantly higher prevalence of PBC in some geographical areas, but no major familial incidence has been communicated in regions with a high PBC prevalence, probably linked to a single water reservoir, when compared with the prevalence in the general population.

Variations in the prevalence of this disease have been recorded in several countries, but no link to any ethnic group has been substantiated. Nevertheless, autoimmune liver disease seems to be more frequent in Northern Europe when compared to Southern Europe or Latin America, but there is still an evident lack of thorough epidemiological studies in many areas of the world. Thus, our present observation of 12 patients belonging to 6 families is even more striking.

PBC or AIH may occur in mother and daughter, father and daughter, sisters, and twins. In our series the association more frequently found was that between mothers and daughters.

In our cohort, one family with a diagnosis of AMA-negative PBC (mother and daughter) was observed. Thus, family association with AMA-negative variant of PBC is also possible, suggesting that both AMA-positive and AMA-negative PBC represent variations of the same disease. To the best of our knowledge, no other family association in AMA-negative PBC patients is so far available in the literature. AMA negative PBC with high titer of antinuclear and/or smooth muscle antibodies with histology compatible with PBC is considered by some authors as a separate disease entity designated autoimmune cholangitis, criteria not accepted by others. The term overlap syndrome between PBC and AIH should be reserved for the rare patients with features of both diseases, associated either simultaneously (in most cases) or consecutively.

Curiously enough, in our series, in 2 patients the association of PBC with AIH in another family member was found. Undoubtedly, genetic predisposition exists in both diseases which share a common pathogenic mechanism. Recently, the development of autoimmune hepatitis following liver transplantation for PBC has been published. This finding represents further evidence of a link between both diseases, as well as does the description of many cases of overlap syndrome between PBC and AIH in patients who show characteristic findings of both diseases, emphasizing the broad spectrum of susceptibility to multiple types of autoimmune liver disease.

Nevertheless, the frequency of published cases of AIH family association has been mentioned as being much lower than those of PBC, a finding not confirmed in the present series in which AIH was found in mother and daughter in three instances and PBC association between mother and daughter in only one instance.

Other autoimmune diseases such as systemic lupus erythematosus (SLE) also show genetic susceptibility to family association. In one of our families, the index case with a cirrhosis related to AIH, SLE was diagnosed several years before the diagnosis of AIH was established, similarly to another report, making the interrelation between all such entities with an immunological background even more complex.

One of the best ways to study the genetic background of autoimmune diseases is to determine the major histocompatibility complex classes I and II. In AIH there is a clear association with class II alleles II DR3 and DR4, and in white hispanics also with HLA class A11. Further studies should be performed in order to evaluate correctly the true prevalence of these associations. Frequent presentation of AIH and PBC in same family speaks in favor of the close association of both autoimmune diseases.

In conclusion, it may be stated that familial association in AIH as well as PBC even if infrequent should not be neglected.

References


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The whole of science is nothing more than everyday thinking.

La ciencia toda no es más que lo que se llega a pensar todos los días.

Albert Einstein (1879-1955)