1130-0108/2003/95/11/752-754
Revista Española de Enfermedades Digestivas

Rev Esp Enferm Dig (Madrid)
Vol. 95, N.° 11, pp. 752-754, 2003

Editorial

The value of serological and genetic markers in inflammatory bowel disease; strength and weakness of the studies

One of the more important aspects for treatment of patients with inflammatory bowel disease is the search for the identification of patient subgroups (1). This is important for the management of acute and sub-acute episodes and for establishing the long term prognosis. In particular, for those patients at risk of frequent relapses. In spite of the introduction in the 1950's of glucocorticosteroids for the treatment of acute attacks which has decreased the mortality rate of the disease, not all patients respond, not even to any of the most sophisticated biological therapies introduced recently. The prevention of relapse and recurrence continues to be a challenge. Thus, the question that the gastroenterologists need to respond is whether we have good markers to identify patient's subgroups and if not, how can we improve the design of our studies to achieve this goal?

Since there is overwhelming evidence that genetic factors play a role in the susceptibility to IBD (2-4) the study of genetic polymorphisms that are involved in the regulation of inflammation, such as HLA and cytokine gene polymorphisms has been the focus of attention.

As stated in the article by the clinical investigators from Valencia in this issue of the Revista Española de Enfermedades Digestivas *(5), the working hypothesis to understand the pathogenesis of these diseases is that chronic inflammatory bowel diseases (IBD) occur as a result of a dysregulated immune response against an as yet unknown factor in a genetically predisposed host. Due to the often observed linkage disequilibrium, whereby alleles located in close proximity are not randomly associated, but occur more frequently together than would be predicted by the individual allele frequencies, one may assume that certain genes are not involved by themselves in disease pathogenesis. They are signalling the presence of other genes that do play a role in determining the heterogeneity of the disease. From this point of view the HLA system and serological markers of the dysregulation of the immune system appear to be good candidates to study.*

*Another reason to investigate genetic and serological markers is the absence of pathognomonic markers for Crohn's disease, ulcerative colitis and for the 10% of cases of colitis that do not belong to either category. This has been recently done by evaluating the value of anti-*Saccharomyces cerevisiae *antibodies (ASCA) and perinuclear antineutrophil cytoplasmic antibodies (pANCA) in order to increase diagnostic accuracy in categorizing intermediate colitis (6).*

It is very likely that both serological markers and genetic factors which have been described in different patient populations, identify subgroups of patients who may not have been properly identified and defined. For example, IgG-pANCA, IgA-

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and IgC-ASCA, antibody against pancreas (PAB) were shown to be independently associated with early age of onset of the disease, as well as fibrostenosing and internal penetrating disease behaviour. Higher pANCA levels were associated with later age of onset of disease and ulcerative colitis-like behaviour. However, the sole monitoring of pANCA, its specificity, and titre determination does not add to the information obtained with standard procedures. The combination of a positive ASCA and a negative pANCA predicts Crohn's disease in 80% of patients with indeterminate colitis and the combination of ASCA-negative and pANCA-positive predicts ulcerative colitis in 63.6% of these patients. Interestingly, 48.5% of patients do not show antibodies against ASCA or pANCA. Most of these patients remain diagnosed with indeterminate colitis during their further clinical course; possibly they form a distinct clinical-serological subgroup (6). However, the combination of pANCA-positive and ASCA-negative in patients with refractory luminal disease may warrant further investigation of the values as to predicting a non-response (7). When compared with healthy controls and patients with infectious enterocolitis, the prevalence of ASCA was significantly increased in patients with Crohn's disease and first-degree relatives (8). The combination of positive ANCA, negative ASCA and negative serum agglutinating antibodies to anaerobic coccoid rods, increased the positive predictive value and specificity in ulcerative colitis. The combination of negative ANCA and positive ASCA with positive antibodies to coccoid rods increased the positive predictive value and specificity in Crohn's disease. In this disease, the presence of positive pANCA was correlated with colonic involvement. No correlation was found be-tween the presence of any of these three different antibodies and the disease activity, the duration, the behaviour of the inflammation or the response to medical treatment (9). The role of these antibodies in the pathophysiology of IBD still needs to be assessed as well as the need to identify the ASCA immunogen(s) that gives rise to the antibody response (10).

The search for biological markers is not easy. Findings of associations of markers with sub-groups of patients are influenced by selection bias, recall bias, misclassification and confounding. The control of confounding risk factors by study design or analysis will enhance comparability of studies (11). The effort to embark in such difficult studies is worthwhile, as Timmer and Sutherland have stated (11), "the overall prognosis of the disease could be improved through lifestyle changes and the prediction of relapse may alleviate the psychological burden that constant fear of incapacitating phases of disease activity poses to the often young and active patient".

However, IBD research in association studies on candidate genes has been characterized by non-replication of results and the inclusion of a limited number of genes. The vision expressed by Tabor et al. in relation to the candidate-gene approach in multifactorial diseases is very relevant in IBD. These authors have argued that the use of epidemiological principles in the selection, analysis and interpretation of candidate genes and DNA sequence variants should also be applied to candidate-gene studies. The biological plausibility, the strength of association, the dose-response relationship and the consistency are the rules of the game (12). According to Tabor et al. (12) et al –"the consistency of the association across past and future studies, and across different populations, is an important consideration. Consistent replication in different populations is strong evidence of causality. Lack of replica-

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tion does not necessarily imply lack of causality, but might point to the need for more studies in certain populations or more detailed study of the function of a particular gene".

It is in this context that we can view the contribution of García Herola and coworkers in this issue of the journal. The authors recognize that the sample size of their study is small and the imperfection of the markers. But it is a beginning of the systematic classification of their patients. The use of good clinical criteria and the long-term follow-up of the patients with the introduction of new genetic and serological markers will contribute to guide treatment decisions and to improve the cost-benefit relationship.

A. S. Peña
Professor of Gastrointestinal Immunology.
Laboratory of Immunogenetics. Department of Gastroenterology.
VU University Medical Centre. Amsterdam, The Netherlands

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