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EDITORIAL

Autoimmune liver diseases

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Abstract

The liver was one of the earliest recognized sites among autoimmune diseases yet autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and their overlap forms, are still problematic in diagnosis and causation. The contributions herein comprise 'pairs of articles' on clinical characteristics, and concepts of etiopathogenesis, for each of the above diseases, together with childhood autoimmune liver disease, overlaps, interpretations of diagnostic serology, and liver transplantation. This issue is timely, since we are witnessing an ever increasing applicability of immunology to a wide variety of chronic diseases, hepatic and non-hepatic, in both developed and developing countries. The 11 invited expert review articles capture the changing features over recent years of the autoimmune liver diseases, the underlying immunomolecular mechanisms of development, the potent albeit still unexplained genetic influences, the expanding repertoire of immunoserological diagnostic markers, and the increasingly effective therapeutic possibilities.

Key words: Autoimmunity; Autoimmune liver diseases; Immunopathogenic processes; Clinical immunology

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The liver is one of the earliest recognized sites among those affected by autoimmune diseases. Such diseases became recognized during the 1950s as novel pathogenetic entities in humans and, later, in laboratory animals. Today there are 80 different disorders attributable to autoimmunity. Over the past five decades, clinical awareness of autoimmune liver disease has been greatly enhanced, knowledge of pathogenesis has become more refined, laboratory diagnosis far more precise, and therapy more effective. These advances are authoritatively described by the expert contributors to this dedicated issue of the *World Journal of Gastroenterology*.

The health burden of autoimmune liver diseases, numerically not of the same magnitude resulting from liver diseases due to alcohol abuse, hepatitis virus infection or steatosis-related pathology, is still very substantial. Thus autoimmune liver diseases can affect individuals in childhood, at highly productive stages of adult life, as well as in later years; and these diseases are life long, and have degrading effects on *joie de vivre* due to distressing symptoms and complications, or side-effects of therapy. Moreover, there is an impression sometimes given by doctors that medical knowledge has not yet fully explained the exact nature or cause of autoimmune disorders. This might not be surprising because autoimmune diseases, including those affecting the liver, result from intricate derangements of immunological functions, and the idea that "immunity" can work against the well-being of the individual is counter-intuitive. Furthermore, immunology as a discipline of science is still not well accommodated in the curricula for students of medicine; it is a fast-evolving and strongly laboratory-based discipline with its own arcane terminology; and it may be disadvantaged by a still incomplete severance from microbiology in many university departments. Expectedly, clinicians may not readily engage with the theoretical pillars of modern immunology, nor fully appreciate the intimate applicability of immunology to a wide variety of chronic diseases, whether in developed or developing countries.

The autoimmune liver diseases considered among these reviews are autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary (autoimmune) sclerosing cholangitis (PSC). AIH and PBC are very well proved in terms of an autoimmune background whereas PSC, as readers will discern, fits less readily into this category. Nevertheless, the evidence in PSC for some forms of immune derangement is quite impressive, and we can reasonably attribute "guilt by association" with, for example, ulcerative colitis, as pointed out by our authors

on this topic.

We have made special provisions in this series of articles on the etiopathogenesis for each of the three autoimmune liver diseases. We often read that "such-and-such" a disease is "an autoimmune disorder of unknown etiology". We would contend that autoimmunity, synonymous with tolerance deficit, should be regarded as aetiology in its own right, meaning that failure of natural immune tolerance itself can be pathogenic even in the absence of any overt environmental provocation. The regular and predictable occurrence of autoimmunity in certain tolerance-deficient inbred and genetically tilted strains of mice (NOD, NZB) is an ample witness to this. Among the autoimmune liver diseases, an environmental provocation is seldom discernible for AIH except for some "transient" examples after exposure to particular sensitizing medications, such as minocycline, whereas for PBC, there are a great variety of agents or processes claimed to act as "initiators". As for PSC, the co-morbidity with ulcerative colitis leads to an indictment of pathogenetic immune hyper-responsiveness to the normally tolerated microbial flora of the colon. Tolerance deficits in humans, as in animals, will be largely genetically based, and deciphering the nature of these errors is an urgent and exciting challenge for the future studies.

Each of the three reviews dealing with etiopathogenesis of an autoimmune liver disease has a partner article on clinical features and management, and readers will note that clinical presentations have changed compared with earlier days. For example, AIH is currently presenting more as an indolent disease with an onset in later life, in contrast to its major impact on young women in the past years. PBC occurs more often at minimally symptomatic earlier stages, with cases frequently ascertained as a result of automated laboratory screening, sometimes for unrelated purposes. It is encouraging for clinicians that both AIH and PBC are gratifyingly responsive to the current standardized treatment regimens, even though, for ursodeoxycholic acid in PBC, the undoubted therapeutic benefits are not readily explicable on theoretical grounds. Finally, some patients will still require liver transplantation for eventual end-stage disease, but readers will be glad to learn that AIH and PBC provide liver transplantation with more satisfying results in terms of post-transplantation morbidity and mortality. And, speaking of transplantation, the inescapable complications of allograft rejection or graft-versus-host disease do exist, but are now eminently manageable. Of much interest, there are credible examples of recurrence of autoimmune liver disease, or even *de novo* autoimmune hepatitis, in an allografted liver. This puzzling immunological scenario is engaged in one of our articles. Finally, a review article focuses on the particular aspects of autoimmune liver diseases occurring during childhood.

We have included an authoritative review on diagnostic serology in autoimmune liver disease. Previously diagnostic serological tests were usually provided by "academic" laboratories in either universities or major teaching hospitals. Currently commercial sectors are providing (increasingly more efficiently) the source materials and/or assay kits for private laboratories to perform autoimmune serologic assays. However, there is still a pressing need for the standardization of the assay procedures worldwide, and for a ready availability of calibrated anti-sera with which the laboratories can evaluate and quantitate their results. Clinicians should also be fully informed about the interpretation of the assay data rather than entirely rely on the printed results from the computer. For example, the hepatologist will be confronted from time to time with what is called an "overlap syndrome". This is a topic that has attracted the attention of authors of several recent review articles, given that the partner diseases, AIH and PBC, or AIH and PSC require different regimens of therapy. The theme is reviewed in these articles. The diagnostic serological laboratory can often help the clinicians to identify the dominant partner to which therapy should primarily be directed.

We recommend to readers this series of reviews as a timely and "state-of-the-art" outline of autoimmunity and liver, by research centres esteemed for their contributions to the science and practice of hepatoimmunology. Finally, we would express our deep appreciation to the invited authors for their painstaking preparation of the highly informative articles in this issue.

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