Etiologic and clinical studies in primary sclerosing cholangitis
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Chapter I

General introduction

For many diseases in the field of gastroenterology and hepatology etiologic factors and pathogenetic mechanisms are known, and efficacious therapies are available. There are several disorders of unknown etiology, yet for which an established cure is available, or vice versa. There are some afflictions about which we have hardly any clue as to their cause and - consequently - do not have a rational therapy to retard or reverse the disease process.

Many factors contribute to the level of understanding of the pathogenesis of a particular disorder. Many diseases exhibit classical patterns, e.g. most infections satisfy Koch's postulates; many hereditary diseases follow clear Mendelian modes of inheritance. Another important factor determining our level of understanding of a disease concerns statistics. Scientific research is basically nothing more than collecting data on observations in a proper and reproducible fashion, and subsequently testing hypotheses on data sets. In order to attain reliable answers one needs sufficiently large sample sizes, and - as important - sufficient funding.

When a disease poses a substantial burden on a population, society will be more willing to channel sizeable funds to relieve this burden. When large numbers of potentially treatable patients hold the prospect of large profits, the same applies for pharmaceutical companies, who nowadays are indispensable contributors to progress in medical therapy.

None of these issues applies to primary sclerosing cholangitis (PSC). This is a rare disease, so there are few patients to investigate and little interest from the major providers of funding for medical research. The relevant pathology lies hidden deep in the body's largest parenchymal organ, the liver. Only after the early 1970s, with the advent of endoscopic retrograde cholangio pancreatography (ERCP), did the true prevalence and spectrum of lesions of PSC become apparent. Before the availability of ERCP, the affected biliary tree could be reached only by laparotomy.
The adjective ‘primary’ indicates its pathogenesis is still elusive, let alone its etiology. It is regarded as a distinct entity, and not secondary to another disease process, such as gallstones. Most experts share the contention that it is an immune-mediated disease, but this term is a rather imprecise description of the pathophysiological process responsible for PSC. Moreover, the phenomenon of mutual citing occurs, which reflects our general lack of understanding about the disease. Indeed, on carefully reviewing potentially relevant findings, the evidence in support of this contention appears, at most, to be circumstantial, and it is clear that other causes have not yet been sufficiently excluded. Thus, in order to make progress in elucidating the cause of PSC, one needs to have an open mind. There may be several different hypotheses of pathogenetic mechanisms that merit serious consideration and investigation.

The aims of this thesis are to provide the reader with insights into several aspects of putative etiologic factors and pathogenetic mechanisms (part two), and clinical management (part three).

Chapter II gives a current perspective of clinical aspects of PSC and proposes some directions for future research, some of which are considered in this thesis.

Chapter III addresses aspects of the concept of genetic susceptibility in relation to inflammatory bowel disease (IBD), illustrated by means of a family case-report.

In chapter IV an attempt is made to elucidate some aspects of the pathogenesis of the inflammation in and around the bile ducts in PSC by studying in detail the composition of the mononuclear cell infiltrate and the possible role of the biliary epithelium as antigen presenting cells.

In chapter V the possibility of an etiologic role for hepatotropic Helicobacters is investigated. In certain strains of laboratory mice several newly recognised murine Helicobacters have been shown to induce chronic hepatitis, cholangitis, and hepatomas, a disease spectrum that resembles that of PSC.

In chapter VI an extensive serological survey is presented. Twenty-two different common viruses as well as Mycoplasma pneumoniae and Chlamydia species are studied as possible predisposing factors for PSC. The association between PSC and Chlamydia species is reported.

In chapter VII the possible association between PSC and Chlamydia species is further evaluated. An attempt at subtyping is made, and the presence of this microorganism in liver tissue from PSC patients is explored. Furthermore, the putative role of anti-Chlamydia-specific heat shock protein antibodies is studied.
There are only three large studies on the natural history of PSC, none of these from The Netherlands. When asked about prognosis, these 1980s-based studies are usually cited. Chapter VIII describes the long-term natural history of 174 Dutch patients with PSC, being the shared second largest reported series in the literature. In addition, some of the clinical characteristics of the disease and the prognostic role of cholangiography are discussed.

Dominant strictures in the major bile ducts are a well-recognized cause of sudden clinical deterioration with acute cholangitis and/or jaundice. Dilatation usually leads to prompt clinical improvement. The optimal mode, route, and duration of treatment of dominant strictures are, however, not established, and depend mainly on local expertise and habit. We prefer endoscopic stenting and advocate to limit the duration of treatment to 1-2 weeks. Experience with this mode of treatment over a four years period is analysed in chapter IX.

Cholangiocarcinoma is the most dreaded complication of PSC, occurring in about 10% of patients. It is associated with a very poor prognosis. To date there are no reliable markers for cholangiocarcinoma and in the setting of PSC its presence is often difficult to differentiate from a common benign stricture. Chapter X investigates the value of brush cytology in detecting cholangiocarcinoma in PSC. Chapter XI provides a summary of this thesis in Dutch.

One can imagine that it is particularly arduous to conduct prospective controlled trials, when dealing with a rare disease with an unpredictable and fluctuating clinical course. Consequently, much of the work presented in this thesis is descriptive or retrospective. However, when so little is known about the etiology and pathogenesis of a disorder, it is imperative to learn as much as possible from careful systematic observations, before embarking on interventional studies. As Louis Pasteur, one of the founders of modern medicine, who would undoubtedly have approved of our quest for microbials as risk factor for PSC, stated more than a century ago: "Le véritable savant n'a pas à s'inquiéter de ce qui peut être dans telle ou telle hypothèse. Son devoir et son but sont de chercher ce qui est."
Chapter III addresses regulatory cytokines and their interactions in the context of inflammatory bowel disease (IBD), illustrated by Th17 and IL-6 as key players. Furthermore, Chapter IV discusses the role of environmental factors in the development of IBD. Research into potential protective factors for IBD is expanded in Chapter V. The association between IBD and Chlamydia species is explored in Chapter VI. The possible association between IBD and Chlamydia species is further studied in Chapter VII. An overview of the entire model is presented in Chapter VIII.