Journal of Autoimmunity 46 (2013) 81–87

Contents lists available at SciVerse ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review

The limitations and hidden gems of the epidemiology of primary biliary cirrhosis

Mauro Podda [a,*], Carlo Selmi [b,c], Ana Lleo [a], Luca Moroni [a], Pietro Invernizzi [a,c]

[a] Liver Unit and Center for Autoimmune Liver Diseases, Humanitas Clinical and Research Center, Rozzano, Milan, Italy
[b] Division of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center, Rozzano, Milan, Italy
[c] Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis, Davis, CA, USA

ARTICLE INFO

Article history:
Received 22 June 2013
Accepted 23 June 2013

Keywords:
Clinical epidemiology
Primary biliary cirrhosis

ABSTRACT

Epidemiology is expected to provide important clues to our understanding of the enigmatic etiopathogenesis of primary biliary cirrhosis (PBC). First, a systematic review of population based studies indicated a wide range in the yearly incidence (0.33–5.8/100.000) and point prevalence (1.91–40.2/100.000) rates. Though different ethnic representations may also contribute it is likely that methodological issues, based on the retrospective survey of diagnosed cases, and time trend play a major role, also in view of the prolonged asymptomatic period of the disease. Of note, the highest prevalence rates (35–40/100.000) were found in areas characterized by high medical awareness and easier access to healthcare. Second, the search for serum AMA in unselected population sera may identify the largest possible number of patients who have or will develop the disease. Indeed, a surprisingly high AMA prevalence rate, ranging between 0.43 and 1%, appears likely in the general population despite the lack of adequate work-up in most studies. Third, the median female to male ratio for PBC is classically accepted as 9–10:1 but is significantly lower for AMA prevalence (2.5:1), death certificates for PBC (4.3:1) and liver transplantation (6:1), thus suggesting that PBC in men may be underdiagnosed in early stages or manifest a more severe progression. Lastly, studies of both PBC and serum AMA prevalence among family members and monozygotic twins strongly support the role played by genetic factors in the etiopathogenesis of the disease. In conclusion, PBC epidemiology is far from being a closed case and the numerous open issues will be solved through a collaborative effort and powerful data mining tools.

1. Introduction

The etiopathogenesis of primary biliary cirrhosis (PBC) remains largely enigmatic despite the well established role of autoimmunity and genetic factors [1–3]. In such uncertainty, epidemiology becomes pivotal in suggesting clues to etiology and to shed light on putative environmental factors which may trigger the disease process in predisposed individuals, similarly to other autoimmune conditions [4–6]. It could be argued that epidemiological data are of major importance for all complex diseases, but we are convinced that this holds particularly true in the case of PBC for its scientific implications and to establish the real burden for healthcare resources of a disease once considered very rare and now significantly more common [7–9]. Indeed, the steep increase in PBC prevalence observed in data collected over time and the wide geographical variations have been the object of discussion [8] and we are convinced that a major role is due to the improved diagnostic accuracy and more complete data collection, favored by easier access to laboratory screening and availability of digitalized medical databases. Nevertheless, in some cases similar methodology changes led to widely variable data in different geographical areas or in groups with different ethnic background in a phenomenon coined geoepidemiology [9–12], thus leaving the crucial questions unanswered and warranting this critical reappraisal of epidemiology papers.

We herein report the results of critical evaluation of the available studies with a specific attention to the recurrent biases responsible for the variability and the limited value of the data. First and foremost, nearly all studies are aimed at establishing the number of patients with a reliable diagnosis of PBC in a definite area. It is therefore clear that the denominator, i.e. the population of the catchment area, may be easily and exactly obtained at any time

* Corresponding author. Liver Unit and Center for Autoimmune Liver Diseases, Department of Gastroenterology, Humanitas Clinical and Research Center, Via Manzoni 56, 20089 Rozzano, Milan, Italy. Tel.: +39 02 82244014.
E-mail address: mauro.podda@humanitas.it (M. Podda).

0896-8411/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jaut.2013.06.015

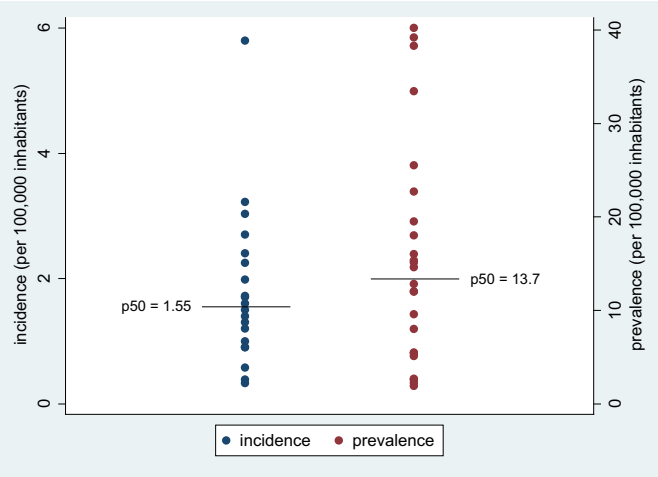

Fig. 1. PBC incidence and prevalence rates [7,15–30].

from census registries, while the numerator, i.e. the number of PBC cases, is largely dependent on a plethora of factors including the location- and time-dependent access to diagnoses in the general population. As a result, we have the ambitious goal to critically discuss the published data and to suggest directions for future research.

2. Prevalence and incidence rates in population-based studies

A comprehensive systematic review of population-based studies for PBC epidemiology was recently published [13]. It followed the checklist proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group [14] to include 24 studies. The review reported PBC incidence and prevalence rates obtained from the population of well defined geographical areas with populations exceeding 100,000 inhabitants. We have updated this search over the next 23 months until December 2012 and included two additional articles fulfilling the above mentioned criteria [15,16]. All studies were case-finding studies, reporting the number of patients with an established diagnosis of PBC in a well defined geographic area, usually corresponding to the catchment area of one or a group of hospitals. Interestingly, in a single area, i.e. the Calgary Health region of Canada, cases were collected from administrative databases used for reimbursement and management purposes [17].

Values of yearly incidence and point prevalence from the 26 papers are illustrated in Fig. 1 [7,15–30]. Both the yearly incidence (0.33–5.8/100.000) and point prevalence (1.91–40.2/100.000) rates manifest a wide variability, with median values of 1.55/100.00 and 13.7/100.00, respectively. Though different ethnic representations might contribute to the high data heterogeneity, we are convinced that methodological aspects and time trend play a preponderant role. This hypothesis is supported by later studies performed with different approaches in the Australian State of Victoria [31,32] and in the Canadian States of Ontario and Alberta [17,33] showing 3- to 10-fold prevalence increases. As somehow expected, the analysis of single articles indicated that higher values of incidence and prevalence were obtained in studies that applied a more rigorous methodology to trace PBC cases. In this regard, the search strategy applied and recommended by the Newcastle group in 1997 [34] is comprehensive and has been adopted by most investigators since its publication. This strategy has its cornerstone in the survey of serum antimitochondrial antibody (AMA) detection in regional laboratories and may have well contributed to the increase over time of PBC incidence and prevalence. Furthermore, medical awareness of the higher frequency of PBC also grew with time and stimulated appropriate testing in a wider number of subjects, usually with mild elevations of serum liver enzymes, even in the absence of symptoms classically associated with PBC such as pruritus. The introduction in many settings of digitalized medical records improved data collection tools and made this approach easier and more reliable in recent years [35]. We are convinced that these factors, taken altogether, should be credited at least partially for the time trend increase of both incident and prevalent cases in more recent papers as well as in those studies spanning through an extended number of years. On the other hand, we note that the improved management of advanced liver disease, the more frequent access to liver transplantation and the widespread use of ursodeoxycholic acid [3] at appropriate doses have clearly prolonged patient survival, thus ultimately affecting PBC prevalence. The obvious fact that these factors are not evenly distributed in different geographical areas reflects the discrepancy of access and expertise in healthcare and may further account for the wide data variability. As an indirect confirmation of this observation, it is noteworthy that the three studies reporting the highest rates for PBC point prevalence (Table 1) the search methods were similar and were performed in different well defined settings that were curiously corresponding to a whole city (Newcastle, UK) [25], county (Olmsted, MN) [28], and country (Iceland) [15]. Among these settings, the city of Newcastle hosts the Academic group which pioneered PBC epidemiology and set the standard for such studies with original and stimulating results, including the most recent one, indicating a seasonal variation in PBC identification [36]. Second, Olmsted country is the site of the Mayo Clinic which has established a network with other county hospitals to create a common database favoring the collaboration for epidemiologic investigations. Third, Iceland has unique conditions for an epidemiologic survey as AMA are measured in a single laboratory that makes it feasible “to select the entire country’s population as a study cohort” [15]. As an indirect confirmation of our hypothesis, remarkably similar point prevalence rates were reported in the three studies with 39.2 cases per 100.000 people in Newcastle, 40.2 in Olmsted County, and 38.3 in Iceland. We are convinced that this homogeneity within studies performed in different settings and at different latitudes but sharing an adequate methodology by highly experienced investigators, suggests that the highest values may represent standard values that can be presently obtained in case finding studies, at least in Westernized countries. Another peculiar aspect of these three studies is the commonly overlooked stability of PBC yearly incidence rates throughout the period of data collection, somehow in contrast with the significant trend of increasing values reported by the large majority of other studies [13] and confirms that in ideal conditions consistent data are found both between and within different studies. The only study based on administrative data in the State of Alberta [17] reported a frequency of PBC that is to be considered among the highest out of individual patient identification studies. Although the use of administrative data is applicable only where healthcare delivery is not fragmented, it represents a promising approach to collect a large volume of information for epidemiology and also for natural history of chronic diseases. This methodology, however, does not overcome the limits of case finding studies which will be discussed in the next section.

3. The limits of case-finding studies

All case finding studies are subject to obvious shortcomings which may influence the resulting incidence and prevalence rates to a variable extent. As already stated in the introduction, all problems reside in the numerator, i.e. the number of diagnoses made and detected in the population of a definite area (the