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Rare statin hepatotoxicity: Convincing evidence based on breakthrough case study

To the Editor:

The excellent study of Björnsson *et al.* [1] published in the February 2012 issue of the *Journal of Hepatology* provides convincing evidence for the existence of rare statin hepatotoxicity. This report clearly contradicts previous statements, which labeled statin hepatotoxicity as a myth and called for a deletion of the packing inserts that contain information about the problem of hepatotoxicity [2].

At different assessment levels, the present statin hepatotoxicity study provides several hallmarks [1]. First, impressive is the high number of 21 hepatotoxicity patients who had a probable or highly probable causality for statins in 14 and 7 cases, respectively. Second, high causality levels in these 21 cases can only be achieved by excellent data that were supplied from spontaneous reports of the Swedish Adverse Drug Reactions Advisory Committee (SADRAC). Third, the strict definition of hepatotoxicity allowed only cases with >5 $\times$ upper limit of normal (ULN) in aminotransferases and/or >2 $\times$ ULN in alkaline phosphatase to be included in their study to reduce the risk of false positive signals. Fourth, with the scale of CIOMS (Council for International Organizations of Medical Sciences), the best available and internationally accepted causality method for hepatotoxicity cases was used. Fifth, among the seven patients with a highly probable causality for statins, there were three cases with a confirmed positive rechallenge test, providing additional support for the existence of statin hepatotoxicity.

The present report provides the rare chance for liver injury studies to describe in detail statin hepatotoxicity as a special disease entity [1]. In previous reports dealing with the characterization of hepatotoxicity, the crucial issue was always whether this approach should also incorporate cases with a possible causality grading or might better be restricted to cases with highly probable and probable causality levels [3,4]. In the present study, the 52 cases with a possible causality for statins were also considered [1]. This raises the question of whether statin hepatotoxicity as assessed under these conditions exhibits characteristics similar to those obtained when only data of cases with highly probable and probable causality levels for statins were used. Calculation of the incidence of statin hepatotoxicity also depends on whether cases with a possible causality are included or not.

Statin hepatotoxicity was correctly determined as the classic idiosyncratic hepatotoxicity [1] and not as intrinsic hepatotoxicity, which is predictable and shows dose dependency, short and consistent latency period, high incidence among users, and experimental reproducibility [5]. This contrasts with the idiosyncratic hepatotoxicity with its low incidence among users at normal doses, long and variable latency period, unpredictability, dose independency, and lack of reproducibility in experimental animals [5]. Attempts to subclassify the idiosyncratic hepatotoxicity by statins into the immunologic or the metabolic subtype have yet to be reported [1]. The immunologic subtype appears unlikely to apply to statin hepatotoxicity since prerequisites such as short duration of exposure of 1–5 weeks, features of overt hypersensitivity, and prompt response to re-exposure with 1–2 doses [5] are not apparent in the reported cases [1]. However, the metabolic subtype with items of variable duration of exposure of one week up to 12 months, the absence of clinical features of hypersensitivity such as rash, fever, and eosinophilia, and the delayed response to rechallenge of many days or weeks [5] best fit with cases of idiosyncratic statin hepatotoxicity [1].

The diagnosis of liver injury by drugs and herbs is often cumbersome to establish, because surrogate markers are lacking [6] and new sophisticated diagnostic approaches have not yet reached the clinical area [7,8]. This is why alternative diagnoses were found and were described in details in numerous hepatotoxicity studies upon thorough causality assessment, as summarized previously [6,9]. In the present study [1], however, primarily missed alternative diagnoses were not mentioned and should have been provided, because this information is helpful also as a reminder to clinicians to evaluate the various differential diagnoses that may otherwise easily be overlooked. For reasons of transparency, also listed details of individual CIOMS items for each case with a highly probable or probable causality for statins would have been appreciated. These few suggestions should not detract from the excellent quality of this highly appreciated statin hepatotoxicity report [1], as will not by no means the associated and somewhat irritating editorial comment that tries to justify ex post own previous unsustainable confusing statements and detracts from the actual topic of statin hepatotoxicity existence [10].

Essentially, this breakthrough case study provides convincing evidence for the existence of rare statin hepatotoxicity and will certainly facilitate assessments of patients with primarily suspected toxic liver injury associated with the use of statins. Statin hepatotoxicity is due to idiosyncrasy of the metabolic subtype, occurs unpredictably and independently of the dose, and is not preventable. Early recognition and statin discontinuation are mandatory for risk management to improve overall prognosis.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Biliary atresia: Does ethnicity matter?

To the Editor:

We wish to call the readership's attention to the recent study by Boonstra *et al.* [1] on the systematic review that showed that the incidence and the prevalence of primary sclerosing cholangitis and primary biliary cirrhosis vary widely based on the geographical distribution. Further, it was previously observed that the severity and the incidence of primary sclerosing cholangitis were influenced by ethnicity [2,3]. We expanded here the scope of this methodology to another biliary disease, i.e. biliary atresia (BA), which is a destructive cholangiopathy of neonates that leads to biliary cirrhosis. Furthermore, it constitutes a public health issue as being the main reason for liver transplantation in children.

Incidence of BA differs between studies. We hypothesized that the incidence of this disease could also be influenced by ethnicity. We thus conducted a systematic literature search to identify articles containing information on the incidence of biliary atresia according to ethnicity. Keywords for the database search of MEDLINE (1840 to January 2012) were "biliary atresia" and "incidence", which were further cross-linked with either "ethnic" or "ethnicity" or "racial" for the search in Google Scholar (Biology and Medicine only). Of 660 references, 96 appeared to contain information related to the topic of interest. References were included in this review if all of the following items were present: time period and location of the study, total live births and number of infants with biliary atresia according to ethnic origin. Incidences of BA were retrieved from the included references, and were plotted on a world map (Fig. 1), which indicates the highest incidence in French Polynesia. We thus combined a population-based observation, and studied the incidence of BA over a time period of 30 years (1979–2009) in Polynesians and Caucasians living in French Polynesia. We found that the incidence of BA at 33.5 per 100,000 live births in Polynesians was significantly higher than in Caucasians ($p = 0.0075$, Fisher exact test) (Fig. 1). From the systematic review, we extracted six other studies [4–9] that reported incidence according to the ethnic origin of the patients. Incidence was high in Polynesians [4,5,10] and native Indians/Inuits [5], intermediate in Asians [6], and low in Caucasians [5,7–9] (Fig. 1). Three of the six studies enabled calculation of the incidence in people of different ethnic origins who share the same geographic location. We found that the incidence of BA was significantly different between Caucasians and Polynesian Maoris in New Zealand [8], Caucasians and native Indians/Inuits in Canada [5], and Caucasians and African-Americans in the United States of America [7] with p-values of 10^{-7}, 10^{-5} and 0.013, respectively (Chi-square test results). Thus, our previous finding that BA was seasonal in French Polynesia [10] suggests that the interplay between ancestry and environment determines the predisposition of Polynesians to BA. As pointed out by Boonstra *et al.* [1], epidemiological data may help identify etiological factors for these complex diseases. Because most epidemiological studies are performed in mixed populations, we propose that future studies on BA and primary sclerosing cholangitis take into account the ethnicity.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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