Hepatitis B vaccine and multiple sclerosis: A case of repeated déjà vu?

To the Editor:

I cannot agree more with Braillon [1] that in revealing the results of any study concerning the adverse reactions of treatment or prevention measures, everyone in the chain of releasing the information should be very prudent. This is especially true in relation to the hepatitis B vaccine.

The unusually low coverage of hepatitis B vaccination in France can be traced to the alleged concerns about the safety of the hepatitis B vaccine. The allegation started right after the country implemented an active hepatitis B vaccination program in 1994–1995 targeting at pre-adolescents in the first year of secondary schools as well as all infants [2]. Initially, the program was highly successful with a coverage rate of 76% in adolescents. During implementation of the program, reports of demyelinating disorders of the central nervous system (CNS) suspected to be associated with hepatitis B vaccination started to appear. Despite the lack of causal association, the issue caught the attention of mass media and, naturally, the general public then. The pressure cumulated became so great that it led the French health authority to suspend hepatitis B vaccination in a school-based program on October 1, 1998. The French government’s decision was immediately condemned by the World Health Organization (WHO) and the French pediatricians [3], because it will very possibly result in a loss of public confidence in hepatitis B vaccination, and thus lead other countries to discontinue its use or decide not to introduce a hepatitis B vaccination program that is critical in the control of hepatitis B worldwide [4]. Indeed, the negative impact could be tremendous, if not handled appropriately. To avoid unnecessary negative impacts to our very successful mass hepatitis B vaccination program in Taiwan [5], right after the suspension of hepatitis B vaccine in France, Taiwan’s Department of Health immediately issued a press release to assure the safety and necessity of hepatitis B vaccination in the country. Fortunately, the French issue did not ferment, and did not affect our program.

A premature or immature release of the results of any study concerning adverse reactions of the hepatitis B vaccines may be exploited by anti-vaccination groups, liability lawyers, and most importantly, the media. Even if the results are disproved finally, the media usually does not report them, because of the loss of news worthiness [6]. The public’s initial wrong image remains, and becomes an obstacle in the implementation of the vaccination program. Unfortunately, despite the rejection of a causal relationship between hepatitis B vaccine and multiple sclerosis [7], reports suggesting a risk of multiple sclerosis associated with recombinant hepatitis B vaccine still appeared [8]. WHO responded quickly by denying the interpretation of the results of the study [WHO Global Advisory Committee on Vaccine Safety, September 2004; http://www.who.int/vaccine_safety/topics/hepatitisb/multiple_sclerosis/sept_04/en/]. The issue recurrently, initiated after an article published by a French group in early October 2008 [9]. Based on subgroup analysis of children having followed the French vaccine recommendations, it was concluded that although hepatitis B vaccination does not increase the risk of CNS inflammatory demyelination in children, the Engerix hepatitis B vaccine appears to increase the risk, especially for the confirmed cases of multiple sclerosis. Although the authors conceded that their results require confirmation in future studies [9], the conclusions of the article very likely have had exerted another negative impact on hepatitis B vaccination, at least in France. The Global Advisory Committee on Vaccine Safety of WHO again responded immediately by concluding that the study did not provide convincing evidence that hepatitis B vaccine, or use of any brand of the vaccine, is associated with an increased risk of acute CNS inflammatory demyelination or multiple sclerosis [WHO Global Advisory Committee on Vaccine Safety, October 8, 2008; http://www.who.int/vaccine_safety/topics/hepatitisb/multiple_sclerosis/oct_2008/en/]. In the meantime, the French health products safety agency (Afssaps) also responded promptly in refuting the association [http://www.
Hopefully, these counteractions will alleviate the low coverage of hepatitis B vaccine in the country.

In the real world, there is no perfect means for a given treatment or prevention that bears no risk. In hepatitis B, any presumed risk of untoward events possibly associated with hepatitis B immunoprophylaxis should be weighed against the disease burden caused by the hepatitis B virus. Education of the public and health professionals is essential [10], and it should include everyone in the chain of releasing the information, right from the sources all the way down to academia and the public.

References


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On the role of platelets in the pathogenesis of viral hepatitis

To the Editor:

We read with interest the commentary by Ulrich Spengler [1] where he evaluated a recent manuscript by Lang et al. [2] on the role of platelet-derived serotonin in the pathogenesis of viral hepatitis. We were somewhat surprised to see that work constituting the foundation of the above-mentioned study was not cited. A few years ago our group started investigating the role of platelets in the pathogenesis of viral hepatitis, using different mouse models that include transgenic mice replicating hepatitis B virus (HBV) at high levels in the hepatocyte and mice infected with hepatotropic adenoviruses and arenaviruses (i.e. lymphocytic choriomeningitis virus [LCMV]). Similar to humans infected with HBV or hepatitis C virus (HCV), liver disease in these models is mostly a consequence of the virus-specific CD8 T cell response aimed at viral clearance. We found that platelets play a previously unrecognized role in viral hepatitis. Upon activation, platelets contribute to liver disease and viral clearance by promoting the recruitment of virus-specific cytotoxic T lymphocytes (CTL) into the liver [3]. Further experiments suggested that this effect depends on specific interactions between platelets and CTL likely occurring within the hepatic microcirculation and helping CTL to extravasate, reach target cells and perform pathogenic and antiviral effector functions [4–6]. We confirmed these results in follow-up studies by showing reduction of hepatic CTL recruitment after pharmacological inhibition of platelet activation [7]. The paper by Lang et al. nicely reiterates a role for platelets in the pathogenesis of liver disease and provides a novel mechanistic hint. They identified serotonin as a potential molecular mediator of CTL recruitment and liver damage in LCMV-infected mice. Although the use of LCMV as a model for human HBV and HCV infection must be taken cautiously (unlike HBV and HCV that infect hepatocytes almost exclusively, LCMV infects primarily non-parenchymal cells of the liver such as Kupffer cells [8]), the study by Lang et al. raises important questions. Where does serotonin come from during liver inflammation? Is it platelet-derived as the authors seem to suggest? What cells respond to serotonin? What serotonin receptors are involved? The answers to these questions are important if we envisage future manipulations of serotonin-dependent pathways...