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Autoimmune hazards of hepatitis B vaccine

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Abstract

According to Hippocratic tradition, the safety level of a preventive medicine must be very high, as it is aimed at protecting people against diseases that they may not contract. This paper points out that information on the safety of hepatitis B vaccine (HBV) is biased as compared to classical requirements of evidence-based medicine (EBM), as exemplified by a documented selectivity in the presentation or even publication of available clinical or epidemiological data. Then, a review is made of data suggesting that HBV is remarkable by the *frequency*, the *severity* and the *variety* of its complications, some of them probably related to a mechanism of molecular mimicry leading to demyelinating diseases, and the others reproducing the spectrum of non-hepatic manifestations of natural hepatitis B. To be explained, this unusual spectrum of toxicity requires additional investigations based upon complete release of available data.

Keywords: Autoimmunity; Evidence-based medicine; Hepatitis B; Molecular mimicry; Vaccination

Contents

Strangely enough, for cost-effective as it is, the pharmaceutical sector of vaccine development remains far from the elementary requirements of evidence-based medicine (EBM) [1]. Whereas personal experience suggested that editors, even in leading medical journal, show a regrettable selectivity in publishing papers on this topics, this has been

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clearly confirmed by the huge delay between the preliminary publication of Hernan's et al. results on the neurological hazards of hepatitis B vaccine (HBV) [2] and their final paper [3] while in the meantime, other investigations of the same team were published and given media coverage without apparent difficulty as they gave good arguments favouring vaccine safety [4]; in parallel, a number of papers of problematic relevance were published to support the safety of HBV vaccine.... Another example: whereas for any person with a minimum of medical awareness, the auto-immune risk of vaccination (and, even more, of *multiple* vaccinations) seems obvious, it is rather strange that the classical duration of safety studies from vaccine development does not go beyond 4 days on average, as performing the majority of clinical trials in high endemic countries does not optimise the guarantee of systematic long-term follow-up [1]. "To be sure, vaccination is starting to emerge as a more complex issue than previously considered" [5].

In a series of important papers [5–11], Shoenfeld et al. have given credibility to the "ugly of vaccination" [5] and shown that it can certainly be considered as "an additional player in the mosaic of autoimmunity" [6]. Regrettably however, clinical evidence supporting their views is difficult to review since, as above mentioned, the game of circulation of information in vaccinotherapy does not comply with the basic EBM rules of transparency, exhaustiveness and differential validation: a number of researchers echoed the reassuring purpose of the French agency about the supposedly negative results of Touzé et al. [12] regarding the risk of multiple sclerosis (MS) after HBV, without noticing that the statistical power of this investigation was inadmissibly low (35% for an odd-ratio of 2...) In contrast, none of them was informed that the same agency performed two case/control studies on the risk of lupus and of Graves' disease after HBV which both gave *statistically significant* results (February 2000 public report) but were never published.

As a medical expert witness specialised in drug monitoring and pharmaco-epidemiology (and unfortunately *not* in immunology or auto-immunity), I have been in charge of an extensive review on the hazards of HBV in the setting of a criminal inquiry currently open in France. If some data are expectedly covered by judiciary secret, the time spent on this topics (probably some 3000 h) gave a unique opportunity to make a thorough inventory of *public* evidence, even if, for the above mentioned reasons, some important data, while open to the public in the form of official communiqués, are not (and sadly do not seem likely to become) available under the academic format of papers published after peer-review. As in the place left below, exhaustiveness will be out of reach, the focus will rather be on a maximum of *transparency* in referencing and critical appraisal of sources, in order to give to every reader a possibility of making for him/herself a more complete review by cross-referencing.[1]

1. An unusual triptyque

As compared to other drugs, especially if their benefit is prevention only, a striking point of HBV hazards emerges from the following triptyque: (1) the *frequency* of its adverse effects; (2) their *severity*; (3) their *variety*.

Regarding the issue of *frequency*, it may be observed that dozens of international papers have been published, totalising hundreds of case reports (which, incidentally, ruins the lame argument that the hypothesis of a specific toxicity regarding this vaccine would result from a new *French paradox*). Although not exhaustive, the REACTIONS database has the advantage of keeping homogenous criteria in its screening of medical literature and, more importantly, of not being limited to English-speaking authors: yet, as early as prior to 1995 (i.e. before any media coverage), this database showed an clear predominance of case reports related to HBV as compared to other vaccines of far greater exposure, such as polio or MMR vaccines. Of course, this predominance has persisted up till now (Table 1).

As another cross-checking and in spite that in France, epidemiological data are scarce, data from the health insurance system showed an impressive, but neglected increase of "serious MS" which coincides

[1] Although still non exhaustive, a more complete list of references is available on the site www.rolandsimion.org.

Table 1
Published case reports on various vaccine hazards in REACTIONS database

Vaccine	Number of case reports	
	Prior to 1995	1983–2004
HBV	42	102
Measle or MMR	20	40
Tetanus or DTP	13	27
Haemophilus influenzae type b	4	7
Polio or DTP	3	3

with the launch of a mass vaccination campaign at the end of 1994 (Fig. 1). Even more evocative is the dramatic evolution of the curve related to "neuro-muscular disorders" from 1996 on, that is just after the first media coverage about HBV vaccine hazards: then, neurologists became quite reluctant to make formal diagnoses of MS in vaccinated people, and experience showed a burst of atypical clinical entities, perfectly reflected by this curve. In parallel, health insurance data showed an increase in the frequency of auto-immune disorders such as lupus, rheumatoid arthritis, etc.

2. Non-neurological hazards

Whereas the *severity* of HBV reported hazards is obvious, their *variety* is exemplified amongst other examples by the series of publications by Geier and Geier [13–21] as well as an investigation by Fisher et al. [22], all of them being devoted to *non*-neurological complications only. Devoted to a case series of 22 patients developing rheumatic disorders after HBV, an early report from Maillefert et al. contained a consistent literature review [23]. A more recent paper (in press) by Shoenfeld et al. contains an impressive record of a variety of published autoimmune complications [24]. Of note also an early alert on the risk of chronic fatigue syndrome [25] which was later refuted [26] but on weak evidence, whereas the single Author's experience collected at least a dozen of cases of post-vaccination fatigue syndrome, in which HBV was by far the most likely cause. A recent preliminary investigation by Poirriez [27] raised interesting hypotheses about the mechanisms of causation regarding the dosages used as well as the route of injection (intramuscular *versus* subcutaneous).

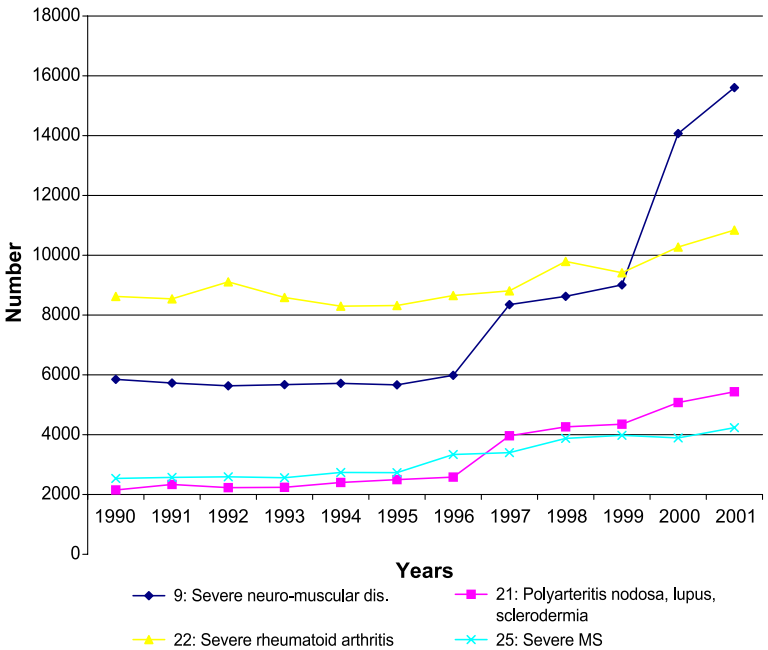

Fig. 1. Data of French health system (CNAM) on the evolution of diseases with a 100% coverage (1990–2001).

3. Neurological hazards

As opposed to methodologically untenable claims of later reviews, strong evidence of post-HBV risk of Guillain-Barré syndrome was given by Shaw et al. [28] from a post-marketing study sponsored by a manufacturer and as such not suspect of an excess in the assessment of risks.

Regarding the risk of MS, the first cases were published in a quite evocative time sequence after the marketing of the first plasma-derived HBV [29,30]; in addition, this risk was rapidly added to the international notice of the first recombinant HBV. That is was related to a background noise related to the high frequency of vaccinated females (nurses, etc.) was discarded by a personal checking in the post-marketing surveillance data of a leading manufacturer of oral contraceptives, a type of products certainly more frequently administered to women than to men.... Frequently evoked as evidencing a lack of MS risk, a study by Zipp et al. [31] was initially assessed by the French agency as deserving to be "discarded" due to its to blatant inconsistencies (February 2000 communiqué). In the same communiqué, methodological weaknesses of Sadovnick and Sheifele [32] paper were rightly emphasised also: the final assessment that in spite of this, their conclusions were "acceptable" corresponded more to a Freudian slip (any conclusion confirming HBV safety is "acceptable") than to any sound evidence-based reasoning. The negative results of the case/control study by DeStefano et al. [33] are weakened by imbalance in patient's neurological history on entry as well as by obscurities in the methods used [33]. Potential biases in Ascherio et al's study [34] have been discussed in further correspondence and the main responsible of the French epidemiological studies on HBV vaccine concluded that at best, American and French results consistently pointed out to an "epidemiologically important increase in risk" [35]. Actually, of the three case/control studies performed by the French agency (only two of them were published [12, 36]), all showed an *increase* of the relative risk of post-HBV demyelinating disorder, lack of statistical significance being only an *expected* consequence of a gross but recurrent lack of power. To the Author's knowledge, the recent results of Hernan et al. [2] showing a *3-fold* increase in the risk of MS was the only epidemiological investigation on this topics which was not hampered by obvious biases or shortcomings. A worrying clue is also given by a cluster of paediatric MS (communiqués of February 2000, March 2001 and May 2002, the youngest listed in French cases being aged of 25 months at the date of diagnosis): the expected rarity of this condition at this age makes the multiplication of observations a regrettable but excellent argument of iatrogenic causality.

4. Conclusion

In HBV documented hazards, two main categories emerge: (1) central demyelinating disorders, most probably related to a mechanism of molecular mimicry, some of them being summarised in [37]; (2) disorders reproducing the non-hepatic manifestation of natural hepatitis B, which leads to question the rationality of injecting viral antigens added with adjuvants in order to protect against an infection where the causative agent is not always cytotoxic by itself, but may act via the formation of antigen-antibodies complexes.

The aim of the present paper was to stimulate research on the unusual toxicity of HBV vaccine and to induce international pressure on health authorities in order to obtain the release of the whole of cumulated clinical and epidemiological evidence in the normal circulation of scientific information and peer-reviewed research.

Take-home messages

- Modern vaccine research and development does not comply with basic requirements of evidence-based medicine (EBM).
- A number of clinical or epidemiological data on the safety hepatitis B vaccine (HBV) have not been published and do not seem to be.
- For a drug used as a prevention, HBV is remarkable by the unusual *frequency*, *severity* and *variety* of its hazards.
- There is an impressive convergence of data given credibility to a potential of this vaccine to induce severe and irreversible central demyelinating disorders.

- A number of clinical and epidemiological data suggest that HBV may reproduce non-hepatic manifestations of natural hepatitis B.
- More research is necessary and there is a need that the scientific community exerts pressure on health authorities to obtain that all existing data become available for peer-reviewed debate.

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