

Hepatitis B vaccine and risk of relapse after a first childhood episode of CNS inflammatory demyelination

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Public concern about possible increases in the risk of multiple sclerosis associated with hepatitis B vaccination has led to low vaccination coverage. We investigated whether this vaccination after a first episode of acute CNS inflammatory demyelination in childhood increased the risk of conversion to multiple sclerosis. We studied the French Kid Sclérose en Plaques (KIDSEP) neuropaediatric cohort of patients enrolled between 1994 and 2003 from their first episode of acute CNS inflammatory demyelination (inclusion in the cohort) until the occurrence of a second episode, up to 2005. A Cox proportional hazards model of time-dependent vaccine exposure was used to evaluate the effect of vaccination (hepatitis B, tetanus) during follow-up on the risk of second episode occurrence (conversion to multiple sclerosis). The cohort included 356 subjects with a mean follow-up of 5.8 years (SD 2.7). Relapse occurred in 146 (41%) subjects during follow-up; 33 subjects were exposed to hepatitis B vaccine and 28 to tetanus vaccine at some time during follow-up. The adjusted hazard ratio (HR) for relapse occurring within 3 years of hepatitis B vaccination was 0.78 (0.32–1.89) and during any time period was 1.09 (0.53–2.24). The adjusted HR for relapse occurring within 3 years of tetanus vaccination was 0.99 (0.58–1.67) and during any time period was 1.08 (0.63–1.83). We conclude that vaccination against hepatitis B or tetanus after a first episode of CNS inflammatory demyelination in childhood does not appear to increase the risk of conversion to multiple sclerosis, although the possibility of a small increase in risk cannot be excluded.

Keywords: child; epidemiology; hepatitis B vaccine; immune-mediated demyelination; multiple sclerosis

Abbreviations: HB = hepatitis B; MS = multiple sclerosis

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Introduction

Several reports have raised the possibility of an effect of recombinant hepatitis B (HB) vaccine on the incidence and severity of multiple sclerosis (MS). Most evaluated the association between immunization and an increase in the risk of incident MS, but found no increase in occurrence in the short (mostly within 2 months) or long term (>1 year) in cohort or case-control designs (Zipp *et al.*, 1999; Sadovnick and Scheifele, 2000; Ascherio *et al.*, 2001; Touzé *et al.*, 2002; DeStefano *et al.*, 2003, 2005). However, most of these previous studies could not exclude small increases in the risk of MS. A recent nested case-control

study in adults reported an association between HB vaccination and an increase in the incidence of MS within 3 years of vaccination (Hernan *et al.*, 2004). The methodology of some of these epidemiological studies has been criticized, due to imprecise case definition or timing (date of diagnosis or date of first symptoms of MS), limited statistical power and a lack of validation of vaccination status (Hernan and Jick, 2006).

The safety of vaccination in patients with MS is another question, which has been evaluated in only one study of a large group of adult patients with established MS,

at different stages of evolution, exposed to HB vaccine a mean of 9.5 years after disease onset (Confavreux *et al.*, 2001). In this study with a case-crossover design, no increase in the risk of subsequent relapse was demonstrated for a 2-month period.

HB vaccination coverage was recently reported to have fallen below 50% in children and adolescents in France, due to public anxiety about possible increases in the risk of MS years after vaccination and despite high levels of morbidity and mortality due to the HB virus worldwide (Kane *et al.*, 1993; Denis, 2004). Moreover, although no official recommendation had been issued, it was widely thought that HB vaccination should be avoided in children who had had an episode of acute CNS inflammatory demyelination, to minimize the risk of relapse and of the subsequent onset of MS.

None of these previous epidemiological studies focused on children or on specific questions about the risk of conversion to MS when immunization follows a first episode of demyelination. Using an observational study based on the KIDSEP neuropaediatric cohort, we investigated whether HB vaccination increases the risk of a second episode, i.e. conversion to MS, in children after a first well-identified episode of acute CNS inflammatory demyelination. We compared the effects of HB vaccination with those of tetanus vaccination, over short- and long-term risk periods.

Material and methods

Design, subjects and source of data

We conducted an observational cohort study among patients with a first episode of acute CNS inflammatory demyelination in childhood from the French national KIDSEP neuropaediatric cohort, evaluating whether risk of relapse was greater after HB vaccine exposure than after tetanus vaccine exposure, if these vaccines were administered after inclusion in the cohort. The inclusion and exclusion criteria of this cohort have been described elsewhere (Mikaeloff *et al.*, 2004a, b, 2006). This cohort included 467 patients with a first episode of acute CNS inflammatory demyelination occurring between January 1, 1990 and December 31, 2003, before the age of 16 years. For the present study, we excluded patients enrolled in the main study before January 1, 1994, because levels of HB vaccination were low in France before that date (Denis, 2004). This resulted in a cohort of 422 patients.

Patients were followed up from inclusion until December 2005, by means of routine clinical visits and regular telephone interviews. Five patients did not complete the follow-up period and no more than 2 years of data are available. However, these data were used in this study (relapses in four of the five patients).

Data collection

Several of the characteristics of the patients (Table 1) were recorded at inclusion, as previously described (Mikaeloff *et al.*, 2004a, b, 2006). Episodes, including a description of symptoms, were all reported by a trained paediatric neurologist. For this particular study, we also included information on economic activity for the head of the family, based on the categories defined

by INSEE (the French National Institute of Statistics and Economic Studies), assessed with a standardized questionnaire (INSEE, 2003). ‘Low economic activity’—corresponding to unemployed people, labourers and low-income employees—was compared with all other categories. Place of residence at inclusion was known for all patients, but we used a dichotomous variable: living within or outside the Parisian region, as the capital city and its suburbs might display specific patterns of health service use. Data were input into a computerized system approved by the ‘Comité National Informatique et Liberté’ (the French data protection agency).

Assessment of exposure to vaccines

All families were contacted by letter and telephone, to provide them with information about the study and to request a copy of the child’s vaccination certificate (‘carnet de santé’). A vaccination was defined as the administration of a commercial preparation of vaccine, whether as a single vaccination or part of a series, and whether for primary immunization or as a booster.

Outcome of the study

The outcome studied was the occurrence of relapse—generally considered as conversion to MS—defined as a second episode of neurological symptoms lasting more than 24 h and then partially or completely stabilized or resolved, as previously described (Mikaeloff *et al.*, 2004a, b, 2006). New symptoms occurring within 1 month of clinical onset were considered to be part of the same episode.

Statistical analysis

Descriptive data were compared, using the χ^2 test or Fisher’s exact test for proportions and the *t*-test or the Wilcoxon test for continuous measures. For the study cohort, time zero was taken as the date on which the first episode of acute CNS inflammatory demyelination was considered to have ended, corresponding to 1 month after the onset of symptoms for the cohort-defining episode. The end-point was the date on which the outcome, relapse, occurred. For event-free subjects, the follow-up period ended on the date of the last known visit.

Cox proportional hazards models were used to evaluate the prognostic value of each vaccination studied and to estimate crude and adjusted hazard ratios (HRs). A time-dependent Cox model was used to assess the effect of each vaccine over time, taking into account the exact date of onset and duration, as recommended in observational studies, to avoid immortal time bias (Suissa, 2003, 2004).

The analysis was adjusted for all the covariates reported in Table 1 potentially affecting the prescription of vaccines and/or outcome. Covariates were separately entered into the model. Analyses were carried out for different durations of exposure to vaccine: 3 and 6 months, 1 and 3 years and for the entire follow-up period after the date of vaccine exposure, to facilitate comparison with results from previous studies considering short- and long-term risk periods.

Results

We excluded 10 patients of foreign origin with different patterns of exposure to vaccination and 56 patients

Table 1 Comparison of characteristics of the study population ($n = 356$) exposed or not exposed to HB or tetanus vaccine after disease onset (first episode)

	No HB vaccine after onset ($n = 323$) n (%) or mean (SD)	HB vaccine after onset ($n = 33$) n (%) or mean (SD)	No tetanus vaccine after onset ($n = 191$) n (%) or mean (SD)	Tetanus vaccine after onset ($n = 165$) n (%) or mean (SD)
Before onset				
Male	142 (44)	17 (52)	77 (40)	82 (50)
Familial MS history	10 (3)	1 (3)	6 (3)	5 (3)
Infection during the month before onset	141 (44)	13 (39)	70 (37)	84 (51)
Low economic activity for the head of the family	149 (46)	17 (52)	77 (40)	89 (54)
Parisian region	98 (30)	16 (49)	61 (32)	53 (32)
At onset				
Age (years)	10 (0.5–16)	11 (0.5–16)	12 (0.5–16)	7 (0.5–16)
Onset after 1997	254 (77)	7 (21)	153 (80)	108 (66)
Polysymptomatic	211 (65)	17 (52)	112 (57)	116 (70)
Transverse myelitis	39 (12)	10 (30)	19 (10)	30 (18)
Optic neuritis	81 (25)	6 (18)	62 (33)	25 (15)
Severe mental status change	117 (36)	9 (27)	51 (27)	75 (46)
Brainstem dysfunction	123 (38)	7 (21)	70 (37)	60 (36)
Oligoclonal bands in CSF*	80 (25)	9 (27)	63 (33)	26 (16)
Cells in CSF $\geq 10 \mu\text{l}$	150 (46)	11 (33)	78 (41)	83 (50)
Proteins in CSF ≥ 500	77 (24)	10 (30)	39 (20)	48 (29)
Child-MS MRI criteria†	117 (36)	9 (27)	86 (45)	40 (24)
Three Barkhof MRI criteria‡	119 (37)	8 (24)	78 (41)	49 (30)
High-dose steroids	194 (60)	12 (36)	123 (64)	83 (50)
Intravenous immunoglobulin	27 (8)	4 (12)	14 (7)	17 (10)
Irreversible disability after inclusion	88 (27)	8 (24)	43 (23)	53 (32)
Prior use of vaccine	150 (46)	8 (24)	191 (100)	162 (98)

*264 patients studied. †Corpus callosum long axis perpendicular lesions or presence of well-defined lesions only (Mikaeloff *et al.*, 2004).

‡Three of four criteria: at least one gadolinium-enhancing T_1 lesion or ≥ 9 T_2 lesions, at least one infratentorial T_2 lesion, at least one juxtacortical T_2 lesion, 3 periventricular lesions (Barkhof *et al.*, 1997).

who did not provide vaccination information from the initial cohort of 422 patients. The study cohort therefore included 356 patients, 350 of whom provided a copy of their vaccination records, the remaining six providing precise vaccination information by telephone. The other 56 French patients (13.6%) who did not participate had a similar frequency of relapse (38% versus 41%) and other variables, but were less likely to be living in the Paris region at disease onset (9% versus 30%) than the participants.

For the study cohort, the mean age at onset was 9.2 ± 4.6 years with an onset before 6 years of age recorded in 109 of the 356 (30.6%) and an onset before 2 years of age recorded in 23 of the 356 (6.5%) patients (see Table 1 for other characteristics at onset). The mean follow-up period for this cohort was 5.8 ± 2.7 years, and second episode occurred during this period in 146 patients (41%). Relapse occurred during the first year for 92 patients (63%) and during the first two years for 115 patients (79%). The symptoms of relapse were multiple ($n = 48$, 33%), transverse myelitis ($n = 3$, 2%), optic neuritis ($n = 42$, 29%), severe mental status change ($n = 11$, 8%) and brainstem dysfunction ($n = 33$, 23%). None of the patients died during follow-up period.

HB vaccination, when administered during follow-up ($n = 33$), was given in isolation [GlaxoSmithKline: Engerix

B[®] ($n = 16$); Aventis Pasteur MSD: GenHevac B[®] ($n = 11$); HB VAX[®] ($n = 5$); Hevac B[®] ($n = 1$)], whereas tetanus vaccination ($n = 165$) was combined with other vaccinations in all but one case [combined with diphtheria and polio ($n = 98$); diphtheria, polio and pertussis ($n = 45$); diphtheria, polio, pertussis and *Haemophilus influenzae* B ($n = 22$)].

The baseline characteristics of patients as a function of vaccine exposure are reported in Table 1: 33 of the 356 (9.3%) patients were exposed to HB vaccine after onset (25 for the first time and eight through booster injections) and 165 patients (46.3%) were exposed to tetanus vaccine (three for the first time and 162 through booster injections). Patients exposed to HB vaccine differed significantly from those not exposed to this vaccine: they were more likely to be living in the Parisian region and to have disease onset before 1997. In most cases, this post-disease onset exposure to HB vaccine was their first exposure to this vaccine (Table 1). Patients exposed to HB vaccine were also more likely to have transverse myelitis at onset, and less likely to have received high-dose steroids as treatment for the first episode. Patients exposed to tetanus vaccine also differed significantly from patients not exposed to this vaccine. They were more likely to have suffered from infections during the month before onset,

more frequently from families of a low socio-economic level, younger at onset and less likely to have a disease onset after 1997 (Table 1).

HB vaccine exposure was not associated with a significant increase in the risk of relapse, regardless of exposure duration (from 3 months to any time since the onset of exposure; Table 2). The adjusted HR for relapse associated with HB vaccine exposure was 0.68 for a 3-month exposure period [95% confidence interval (CI): 0.09–4.98], 0.78 for a three-year exposure period (95% CI: 0.32–1.89) and 1.09 for any time period (0.53–2.24). Relapses were recorded within 3 years of exposure in six patients vaccinated against HB, and during any time period in 10 such patients: the upper limit of the 95% CI could exclude increases of 1.9 times (for the 3-year period) and 2.3 times (for the any time period), but not a lower increase. Confounding factors potentially accounting for the difference between crude and adjusted HR values included the presence of optic neuritis at onset, child-MS MRI or Barkhof MRI criteria and oligoclonal bands in CSF analysis. Tetanus vaccine exposure was not associated with a significant increase in the risk of relapse, regardless of the duration of exposure studied (Table 2).

Discussion

We provide, for the first time, an evaluation of the potential risk of second episode occurrence, i.e. conversion to MS, associated with administration of the HB and tetanus vaccines after a first episode of acute CNS inflammatory demyelination. This study was carried out in children, a population with a higher exposure to vaccines than adults, who had not previously been analysed.

Previous studies, concerning association between HB vaccine exposure and increase of MS incidence, concerned the general population. Our population of first episode of CNS inflammatory demyelination could be more susceptible to the effect of a studied potential risk factor, such as HB vaccine. Only one other epidemiological study has been published to date on the safety of vaccinations in patients with MS. This previous study had a different design—evaluating patients with long-term MS, at different stages, some of whom were in the secondary progressive course, and evaluating the risk of relapse in a 2-month short-term risk period, in a case-crossover design (Confavreux *et al.*, 2001). No increase in the risk of relapse was found to be associated with exposure to HB vaccine (15 of 643 MS patients were exposed within the 2-month risk period before the index relapse; relative risk: 0.67, 95% CI, lower limit: 0.20, upper limit 2.17). This led to the recommendation issued by the American Academy of Neurology that patients with MS should follow Centers for Disease Control indications for immunization in the general population for all vaccinations, including HB vaccine (Rutschmann *et al.*, 2002). However, this recommendation did not take into account the specific issues of vaccination in the early phase

of the disease and in children. Moreover, a recent study by Hernan *et al.* (2004) reported an increase in the risk of MS incidence within 3 years of vaccination (in this study, 11 of the 143 MS cases were exposed to HB vaccine within the 3-year risk period), suggesting that risk periods longer than 2 months should be evaluated in studies on vaccination safety in MS patients.

The paediatric context of our study is one of its strong points. It is based on a large, recognized cohort of children and adolescents from an ongoing study (not focusing on vaccination), with a long period of follow-up. Precise dates and descriptions were provided by a paediatric neurologist for both first and second episodes, and the risk of underreporting of episodes was minimized by exhaustive inclusions in participating centres (Mikaeloff *et al.*, 2004a, b, 2006). This made it possible to circumvent previously identified methodological limitations and to minimize potential bias due to the time elapsed from the onset of the first symptoms and the onset of MS or its diagnosis (Naismith and Cross, 2004; DeStefano *et al.*, 2005; Hernan and Jick, 2006).

Another strength of this study is that vaccination status was validated, in most cases, by a paper copy of the vaccination certificate, as recommended (Chen *et al.*, 2005). The risk of vaccination not being specified on the certificate was very low because all vaccinations must be recorded on this document (the ‘carnet de santé’) in France (Denis, 2004). Moreover, the ‘carnet de santé’ is highly valued by families, is presented systematically to the physician at all medical consultations during follow-up and contains certificates opening access to maximal reimbursement by the universal health insurance system.

The exclusion of patients for whom a copy of the vaccination certificate was not obtained might have introduced a bias, because the probability of exposure may depend on the geographic and economic activity of parents (Denis, 2004). However, analyses were adjusted for geographic differences, the socio-economic level of parents, the aggressiveness of initial disease and other previously described predictors of relapse (Mikaeloff *et al.*, 2004a, b). Time was rigorously taken into account, using multivariate survival analysis and time-dependent vaccine exposure, and considering various durations of follow-up in the cohort and timing and duration of vaccine exposure.

Analyses were performed for several different durations of vaccine exposure: 3 and 6 months, 1 and 3 years and the entire follow-up period after vaccination. This aspect is particularly important because MS has a variable rate of relapse over time and the true risk period after HB vaccination has not been established (Compston and Coles, 2002; Mikaeloff *et al.*, 2004a, b; Strohm, 2005). The time sequences of white matter and axonal destruction in MS following stimulation with external antigens, such as vaccines, has also not been defined (Piaggio *et al.*, 2005; Schattner, 2005). We considered the 3-year risk period specifically due to the report of an association with an

Table 2 Cox survival analysis of the effect of HB or tetanus vaccine exposure on relapse (second episode)

Vaccine exposure after onset	Number of subjects with a relapse	Crude HR*	Adjusted HR* [†] (95%CI)	P-value
Hepatitis B (HB)				
None (n = 323)	136	1	Reference	–
HB exposed any time (n = 33)	10	1.24	1.09 (0.53–2.24)	0.82
Time period studied after vaccination				
First three months	1	0.78	0.68 (0.09–4.98)	0.70
First six months	1	0.48	0.38 (0.05–2.79)	0.34
First year	2	0.59	0.46 (0.11–1.96)	0.30
First three years	6	0.99	0.78 (0.32–1.89)	0.58
Tetanus				
None (n = 191)	118	1	Reference	–
Tetanus exposed any time (n = 165)	28	1.06	1.08 (0.63–1.83)	0.79
Time period studied after vaccination				
First three months	3	0.69	0.79 (0.25–2.50)	0.69
First six months	8	1.08	1.22 (0.59–2.53)	0.60
First year	11	0.89	0.97 (0.51–1.84)	0.92
First three years	21	0.96	0.99 (0.58–1.67)	0.96

*HR = hazard ratio, no HB vaccine exposure is the reference group. [†]Adjusted on all covariates of Table 1.

increase in MS incidence during this time period in a recent study (Hernan *et al.*, 2004).

We found that HB vaccination did not increase the risk of relapse and conversion to MS, either within 3 years of vaccination or at any time point after vaccination, in subjects with first episode of CNS inflammatory demyelination in childhood. However, a certain lack of power should be taken into account when interpreting our results. Indeed, only six patients relapsed within 3 years, and 10 within the entire follow-up period. The upper boundary of the 95% CI indicates that increases in risk by a factor of 1.9 (for the 3-year period) and 2.3 (for the any time period) could be excluded, but that it is not possible to exclude a smaller increase in risk. Our study had the same magnitude of statistical power than previous studies. Finally, the risk of an initial episode of demyelination after HB vaccination in childhood requires further study.

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