A case-series of adverse events, positive re-challenge of symptoms, and events in identical twins following hepatitis B vaccination: analysis of the Vaccine Adverse Event Reporting System (VAERS) database and literature review

M.R. Geier, D.A. Geier

The Genetic Centers of America, MedCon, Inc., Silver Spring, Maryland, USA

Abstract

Objectives

Adverse events and positive re-challenge of symptoms reported in the scientific literature and to the Vaccine Adverse Event Reporting System (VAERS) following hepatitis B vaccination (HBV) were examined.

Methods

The VAERS and PubMed (1966-2003) were searched for autoimmune conditions including arthritis, rheumatoid arthritis, myelitis, optic neuritis, multiple sclerosis (MS), Guillain Barré Syndrome (GBS), glomerulonephritis, pancytopenia/thrombocytopenia, fatigue, and chronic fatigue, and Systemic Lupus Erythematous (SLE) following HBV.

Results

HBV was associated with a number of serious conditions and positive re-challenge or significant exacerbation of symptoms following immunization. There were 415 arthritis, 166 rheumatoid arthritis, 130 myelitis, 4 SLE, 100 optic neuritis, 101 GBS, 29 glomerulonephritis, 283 pancytopenia/thrombocytopenia, and 183 MS events reported following HBV. A total of 465 positive re-challenge adverse events were observed following adult HBV that occurred sooner and with more severity than initial adverse event reports. A case-report of arthritis occurring in identical twins was also identified.

Conclusions

Evidence from biological plausibility, case-reports, case-series, epidemiological, and now for positive re-challenge and exacerbation of symptoms, and events in identical twins was presented. One would have to consider that there is causal relationship between HBV and serious autoimmune disorders among certain susceptible vaccine recipients in a defined temporal period following immunization. In immunizing adults, the patient, with the help of their physician, should make an informed consent decision as to whether to be immunized or not, weighing the small risks of the adverse effects of HBVwith the risk of exposure to deadly hepatitis B virus.

Key words

Arthritis, autoimmunity, Guillain Barré syndrome, Hepatitis B vaccine, multiple sclerosis, VAERS.

Mark R. Geier, MD, PhD, President, The Genetic Centers of America; David A. Geier, President, MedCon, Inc.

Funding: There was no funding source for this research.

Conflict of Interest: Dr. Mark Geier has appeared as an expert witness and as a consultant in cases before the US National Vaccine Injury Compensation Act and in civil litigation involving vaccine adverse reactions, and David Geier has been a consultant before the US National Vaccine Injury Compensation Act and in civil litigation involving vaccine adverse reactions.

Please address correspondence and reprint requests to: Mark R. Geier, MD, PhD, President, The Genetic Centers of America, 14 Redgate Court, Silver Spring, Maryland 20905, USA.
E-mail: mgeier@comcast.net

Received on April 19, 2004; accepted in revised form on July 16, 2004.

Introduction

Genetically engineered hepatitis B vaccines, developed and licensed in the 1980s in the United States, are most commonly produced by inserting the gene for HBsAg into the yeast *Saccharomyces cerevisiae* (1, 2). Following growth of the yeast, vaccine is prepared by lysing the yeast to free HBsAg particles, which are separated from yeast components by biochemical and biophysical methods. Two recombinant vaccines produced in yeast (Merck, Recombivax; SmithKline Biologicals, Energix) are available in the United States and many countries worldwide.

The purpose of this study was to examine cases of adverse events reported in the scientific literature and to the Vaccine Adverse Event Reporting System (VAERS) database following hepatitis B vaccine administration. In addition, we also evaluated the scientific literature and the VAERS database for cases describing positive re-challenge or significant exacerbation of symptoms reported following hepatitis B vaccination.

Methods

A retrospective examination of the VAERS database was undertaken using Microsoft Access. The VAERS database is an epidemiological database that was created by an Act of the U.S. Congress and has been maintained by the Centers for Disease Control and Prevention (CDC) in Atlanta, GAsince 1990. Specific vaccine-associated adverse events are to be reported to this database as mandated by law. The CDC requires written and telephonic confirmation of serious adverse events and follows-up these patients one year latter to determine if they have recovered. The Food and Drug Administration (FDA) inquires into deaths reported to the VAERS database by contacting the patient's healthcare provider and physician. The FDA also monitors the VAERS database to determine if any vaccine or vaccine lot has a higher than expected incidence rate of adverse events reported. We, the VAERS Working Group of the CDC, and the FDA all analyze and publish epidemiological studies based upon examination of the VAERS database.

The strength of the VAERS database stems from its large reporting base (i.e. patients from the entire United States). Additionally, the VAERS Working Group of the CDC has previously reported that less than 5% of adverse events are reported by parents. The potential weakness of the VAERS database is that not all vaccine-associated adverse events in practice are reported. Additionally, because the VAERS database is a registry of vaccine-associated adverse events, it is not possible in examination of the VAERS to obtain the full medical histories of patients reporting adverse events.

In our literature search, we searched PubMed (1966-2003) to determine the number of case reports, or case-series of serious autoimmune disorders reported following hepatitis B immunization. The serious conditions searched in the literature following hepatitis B immunization included arthritis, rheumatoid arthritis, Systemic Lupus Erythematosus (SLE), optic neuritis, Guillain Barré Syndrome (GBS), glomerulonephritis, pancytopenia/thrombocytopenia, and myelitis. The literature search using PubMed (1966-2003) was also extended to examine all case reports, or case-series of serious conditions in which patients exhibited positive re-challenge or significant exacerbation of symptoms following successive doses of hepatitis B vaccine.

In examining the VAERS database, we evaluated reports of autoimmune conditions including arthritis, rheumatoid arthritis, myelitis, optic neuritis, multiple sclerosis (MS), GBS, glomerulonephritis, pancytopenia, and thrombocytopenia. In evaluating these serious conditions in the VAERS, the total number of reports, male/female reports, median onset time in days, median age in years, and percent disabled (a VAERS database field) were evaluated. We also examined reports generated following hepatitis B vaccination in which positive re-challenge was described in the VAERS database. The types of positive re-challenge adverse events we examined following hepatitis B vaccination included: arthralgia, arthrosis, arthritis, neuritis, fatigue,

chronic (based upon a one year follow-up) fatigue, myalgia, gait abnormalities, neuropathy, tremor, GBS, flu syndrome, erythema multiforma, and alopecia. These types of adverse events were based upon descriptions of those reporting them and defined fields contained within the VAERS database.

Results

In Table I and Table II are a summary of the case-reports of adverse events that have been reported following hepatitis B immunization in the scientific literature and in the VAERS database. It was observed that serious adverse events have been reported primarily among adult male and female hepatitis B vaccine recipients within several weeks of immunization. There were a number of serious adverse events reported following hepatitis B vaccine that resulted in disabilities. In addition, Meyboom *et al*. have reported the WHO Collaborating Centre for International Drug Monitoring has, from National Pharmacovigilance Centers in several countries received 28 cases of thrombocytopenia possibly related to hepatitis vaccine (different brands) (33).

A review of the VAERS database indicated that there were 465 reports of positive re-challenge following hepatitis B vaccination among those residing in the United States. Among the 465 reports examined 301 were classified as occurring in females, 148 in males, and in 16 reports the sex was not specified. The overall median age was 19.5 years and the overall median onset was 1 day. There were a total of 166 Emergency Department visits, 7 life-threatening reactions, 26 hospitalizations (median hospital visit = 4 days), 21 disabilities, and 1 death. In addition, a review of the 465 reports indicated that in 87 reports the patients had not recovered, in 107 reports the recovery status was uncertain, and in 271 reports the patients had recovered.

Table III summarizes muscular/skeletal, neurological and immunological positive re-challenge adverse events reported to the VAERS database following hepatitis B vaccination. This table shows that in general adult hepatitis B vaccine recipients tended to report positive re-challenge adverse events to the VAERS database within a few days to weeks following hepatitis B vaccination. In addition, a significant level of disability was reported among those reporting positive re-challenge hepatitis B vaccine associated adverse events, especially among those reporting arthritis (38%), neuropathy (50%) and chronic fatigue (27%). Table IV summarizes positive re-challenge or significant exacerbations of reactions after recombinant hepatitis B vaccine in the scientific literature.

In addition to the information shown in Table IV, Hassan and Oldham have reported that SmithKline Beecham Pharmaceuticals has received 11 reports of re-challenge in people who developed joint symptoms after receiving Engerix-B; six of them developed polyarthralgia again, and in most of them re-challenge led to more severe symptoms (40). Maillefert *et al*., have reported on six women (age range: 25 to 45 years) developing inflammatory

Table I. Summary of serious conditions reported after hepatitis B vaccine in the scientific literature.

Type of condition	Total number of reports	Female/male ratio	Median age (years)	Median onset (days)	Reference #
Arthritis	8	0.60	36	14	3-8
Rheumatoid arthritis	13	2.2	44	14	4, 9-11
Systemic lupus erythematosus	4 (all female)	-	24.5	10.5	8, 12, 13
Optic neuritis	4	1.0	43	7.0	10, 14, 15
Guillain Barré syndrome	8	3.0	36	6.0	10, 16-20
Glomerulonephritis	3	0.50	21	25	21-23
Pancytopenia/thrombocytopenia	10	1.0	15	29.5	10, 24-26
Myelitis	10	2.3	36.5	21	10, 27-32

Table II. Summary of serious conditions reported after hepatitis B vaccine in the VAERS database.

Type of condition	Total number of reports	Female/male ratio	Median age (years)	Median onset (days)	Percent disabled
Arthritis	407	3.2	38	6	18
Rheumatoid arthritis	153	3.2	36	28	47
Myelitis	120	2.2	34	22	36
Optic neuritis	96	2.2	33	13	36
Multiple sclerosis	183	2.4	33.5	36.5	36
Guillain Barré syndrome	93	1.5	34	18	26
Glomerulonephritis	26	2.4	25	9.5	10
Pancytopenia	11	0.83	33	34	0
Thrombocytopenia	263	1.0	13	12	5.7

Table III. Positive re-challenge adverse events reported to VAERS following hepatitis B vaccination.

Type of adverse event	Number of male reports	Number of female reports	Median age	Median onset	Percent disabled
Arthritis	4	4	27	12	38
Arthralgia	10	38	36	2	14
Arthrosis	3	5	36	0	25
Myalgia	15	41	34	1	3.6
Neuropathy	1	3	38	10	50
Fatigue	11	21	30	2	12
Chronic fatigue	2	9	34	8	27
Personality disorders	0	5	16	0	0
Tremor	2	6	7	1	0
Guillain Barré syndrome	0	1	34	-	0
Flu syndrome	9	26	34	0	5.7
Erythema multiforma	3	0	34	0	0
Alopecia	0	10	18	6	10

polyarthritis diagnosed as rheumatoid arthritis (41). They had received immunization 1 to 20 days prior to symptom onset (mean onset: 9 days). All received another injection. The symptoms worsened in four cases, were not modified in one, and were unknown in one patient. These patients were followed-up for between 3 months and 6 years. The follow-up of each patient revealed persistent symptoms, despite all patients being treated with at least one disease-modifying anti-rheumatic drug, including methotrexate for four. Joint erosions were also shown to have occurred in three out of four patients followed-up for >1 year. Mallefert *et al*. also reported on five women (mean age = 19) that developed arthritis within several weeks following hepatitis B vaccination. In three cases, a further hepatitis B vaccination was administered. This additional vaccination resulted in the worsening of arthritis in all three cases. Tartaglino *et al*., have reported on a case of a 40-year-old male who presented with a 6-week history of progressive lower-extremity numbness and difficulty walking (42). Symptoms began 2 weeks after receiving the first dose of hepatitis B vaccine. The patient was administered a second dose of hepatitis B vaccine, and one month latter the sensory disturbance ascended to the nipple level and the patient had difficulty walking. A physical examination of the patient showed that the patient had markedly impaired proprioception and vibration sense, minimal weakness, hyporeflexia in the lower extremities, and a T-4 sensory level. The patient upon follow-up was left with residual neurological deficits. Pope *et al*. described two patients that developed arthralgias following their initial doses of hepatitis B vaccine (11). Subsequently, one patient (a 47-year-old male) developed rheumatoid arthritis 14 days following a second dose of hepatitis B vaccine, and the other patient (a 57-year-old female) developed rheumatoid arthritis less than 10 days following a second dose of hepatitis B vaccine.

Guis *et al.* have described identical twin sisters who developed arthritis following hepatitis B vaccination (44). The first sister's medical history was unremarkable until December 1993, when following her third and final injection of hepatitis B vaccine she began complaining of arthritis. On physical examination, arthritis involving both wrists and the proximal and distal interphalangeal joints of the hands and feet were noted. Arthritis was associated with myalgias and upper limb muscle weakness. The twin sister had a similar clinical presentation with bilateral arthritis of wrists, shoulders, temporomandibular joints, hands, and ankles following her third hepatitis B vaccination in 1997. Her medical history was unremarkable except for mild asthma and high blood pressure. On admission, she reported peripheral arthritis with myalgias. Neurological examination showed distal paresthesias and cramps of the 4 limbs, severe weakness of the hand muscles, hyperreflexia of the right upper limb, right Hoffmann's sign, and normal plantar reflexes of micturition.

Discussion

This analysis revealed that hepatitis B vaccination has been associated both in the VAERS database and in the scientific literature with a number of cases of serious conditions, positive re-challenge or significant exacerbation of symptoms, and adverse events in identical twins following immunization. Our review of the VAERS database indicated that positive re-challenge adverse events were primarily observed among adult hepatitis B vaccine recipients within a few days to weeks following immunization, and tended to be rather severe considering the large percentage of disabilities observed among some of the types of adverse events examined. Our literature review also showed that hepatitis B vaccine administration has been associated with a number of positive re-challenge and significant exacerbation of symptoms following immunization, primarily among adult vaccine recipients within a few days to weeks following immunization, and that very often positive re-challenge reactions were more severe than previous reactions.

The biological basis for serious adverse events following hepatitis B vaccination has been described in several studies. McMahon *et al*. have described that adverse reactions to hepatitis B vaccine are due to thimerosal, a mercurial compound that is used as a preserv-

Table IV. Summary of positive re-challenge or significant exacerbations of reactions after recombinant hepatitis B vaccine in the scientific literature.

Reaction	Sex	Age	Dose no.	Onset	Duration	Reference no.
Fatigue-myalgias-eye pain	F	61	1	1 day	Several days	34
Fatigue-anorexia-headache-weight loss-renal vasculitis			2	Rapid	2 years (resolved with kidney transplant)	-
Myalgia-joint pain-morning stiffness	M	45	1	14 days	1 month	35
More severe arthralgia and myalgia-polyarteritis nodosa			2	-	7 months (resolved with right hand amputation)	-
Rash	M	38	5	-	Several days	35
Fatigue-burning eyes-pityriasis rosea-like eruption			6	2 days	Several weeks	-
Pain and swelling of the right wrist	F	20	1	4 days	Several months (resolved completely)	4
More severe pain and swelling			2	Several days	Several months	-
Transient weakness of the left leg	F	19	2	3 months	Several weeks	36
Arthralgias-left sided hemihypesthesia -unstable gait			3	7 days	1 year	
Thrombocytopenia purpura	F	21	1	28 days	4 months	10
Thrombocytopenia purpura			2	28 days	2 months	-
Acute glomerulonephritis	F	12	1	14 days	3 days (resolved completely)	37
Chronic glomerulonephritis			2	14 days	3.5 years	-
Leukoencephalitis	F	39	2	28 days	Several months (markedly improved condition following neuro-surgery)	38
Leukoencephalitis			3	11 days	Several months	-
Arm-leg rash	F	16	1	Several days	-	39
Weakness-gait disturbance-gastro-intestinal disorders-weight loss			2	30 days	Several years (mildly symptomatic 8 years post-diagnosis)	-

ative in the vaccine, or to the aluminum hydroxide (alum) used as an adjuvant (45). We have previously reported that the combination of thimerosal, aluminum hydroxide, yeast (and other extraneous proteins) and the hepatitis B surface antigen, may work synergistically to produce severe adverse reactions in susceptible hepatitis B vaccine recipients (10). Rietschel and Adams have reported a case in which a 29 year-old underwent patch testing and was found to be strongly positive to thimerosal (46). He was subsequently administered a dose of hepatitis B vaccine containing thimerosal, and within 6 hours following immunization he developed severe dermatitis that spread over a significant potion of his body which lasted for many months following immunization. The authors concluded that although thimerosal is present in hepatitis B vaccines at a concentration of only 1:20,000, it clearly can induce severe cutaneous reactions of the delayed hypersensitivity type. The authors also concluded that although not all thimerosal-sensitive patients develop adverse reactions following immunizations containing thimerosal, there is a potential risk with such vaccinations, and the reactions can be very long lasting. In addition, Pennesi *et al*. have described a case-report of positive re-challenge for glomerulonephritis following hepatitis B vaccination, in which a renal biopsy was performed and demonstrated mesangial proliferative glomerulonephritis with IgA deposits, similar to what has been described in natural hepatitis B virus-related glomerulonephritis (37). They also performed an immu-

nohistochemical examination of the biopsy using monoclonal antibodies against hepatitis B surface antigen and hepatitis B core antigen, and demonstrated that the hepatitis B surface antigen was present in renal tissue and in the tubular and peritubular zones.

We have recently published a review of hepatitis B vaccination (10). In our review, we analyzed 33 case-reports of adverse events reported following hepatitis B vaccination. We found that the adverse events we analyzed were reported in adults within a few days to weeks following immunization, and that symptoms persisted for prolonged periods of time. In our review of the epidemiological evidence for serious adverse events reported following hepatitis B vaccination, we determined that adults from a few days to weeks following immunization were at statistically significant increased risk for the incidence rate of reported serious arthritic, neurological, immunological, and gastrointestinal adverse events to the VAERS database (10). We have determined the following incidence rates of significant adverse events reported to the VAERS database following adult hepatitis B vaccination, including: arthritis (1.4 per million hepatitis B vaccinations), myelitis (0.56 per million hepatitis B vaccinations), thrombocytopenia (0.80 per million hepatitis B vaccinations), GBS (0.43 per million hepatitis B vaccinations), and hepatitis (0.56 per million hepatitis B vaccinations) (47). We concluded our review by stating that adult hepatitis B vaccine recipients were at increased risk for autoimmune disorders within a defined temporal period following immunization, suggesting that hepatitis B vaccine is not the leading cause of serious autoimmune disorders in whole populations studied for temporal periods of many years following vaccination (10). This result appears to have been confirmed by a recent study of the CDC examining the Vaccine Safety Datalink (VSD) database (48). In the CDC study, they reviewed adverse events reported following adult hepatitis B vaccination, and determined that demyelinating diseases (Odds Ratio = 0.8; 95% Confidence Interval: 0.8-3.0) were not statistically significantly increased in comparison to the background incidence rate in the year following immunization.

Therefore, the evidence for the ability of hepatitis B vaccination to cause serious autoimmune adverse events in a defined temporal period following immunization has been presented in the form of biological plausibility, case-reports, case-series, epidemiological, and now for positive re-challenge and exacerbation of symptoms and adverse events in identical twins following hepatitis B vaccination. In further support of the notion that hepatitis B vaccine can cause serious autoimmune adverse events, authors have described under what potential conditions other vaccines may induce serious autoimmune adverse events in susceptible vaccine recipients (49).

In considering whether a vaccine can cause a specific type of adverse event, Pirmohamed and Winstanley have described that causality can be inferred from several points including the temporal relationship between the start of drug and onset of symptoms, whether symptoms resolve on drug withdrawal, any history of re-challenge, any previous reports of similar side-effects, and biological plausibility (50). We believe that in light of evidence from such a multitude of different and independent sources showing serious autoimmune adverse events following hepatitis B vaccination, one would have to consider that there is causal relationship between hepatitis B vaccination and serious autoimmune disorders among certain susceptible vaccine recipients in a defined period following immunization.

We believe, considering the potential for serious adverse events following hepatitis B vaccination, that adult vaccine recipients should make an informed consistent decision as to whether to be immunized or not. In making a decision, physicians and patients should analyze the relatively small, but apparently real risk of hepatitis B vaccination to cause serious autoimmune disorders in vaccine recipients, the benefits of hepatitis B vaccine in preventing the deadly disease of hepatitis B (the risk of which is highly dependent upon the lifestyles of vaccine recipients), and conduct a thorough review of the patient's past clinical history.

We suggest that those rare individuals that do indeed develop a serious adverse event following hepatitis B vaccination in the US should be advised that they may be eligible for compensation from the no-fault National Vaccine Injury Compensation Program. The patient's physician should make a concerted effort to report their patient's adverse event as thoroughly as possible to the VAERS database, so that further information may be gleaned about the safety of hepatitis B vaccination. We also suggest that further studies should be conducted to further investigate the actual case-histories of those experiencing adverse events following hepatitis B vaccination.

References

1. EMINI EA, ELLIS RW, MILLER WJ, MCALEER WJ, SCOLNICK EM, GERETY RJ: Production and immunological analysis of recombinant hepatitis B vaccine. *J Infect* 1986; 13 (Suppl. A): 3-9.
2. STEPHENNE J: Development and production aspects of a recombinant yeast-derived hepatitis B vaccine. *Vaccine* 1990; 8 (Suppl.): S69-73.
3. ROGERSON SJ, NYE FJ: Hepatitis B vaccine associated with erythema nodosum and polyarthritis. *BMJ* 1990; 301: 345.
4. GROSS K, COMBE C, KRUGER K, SCHATTENKIRCHNER M: Arthritis after hepatitis B vaccination. Report of three cases. *Scand J Rheumatol* 1995; 24: 50-2.
5. BRACCI M, ZOPPINI A: Polyarthritis associated with hepatitis B vaccination. *Br J Rheumatol* 1997; 36: 300-1.
6. CATHEBRAS P, CARTRY O, PROUST MH *et al.*: Arthritis, hypercalcemia, and lytic bone lesions after hepatitis B vaccination. *J Rheumatol* 1996; 23: 558-60.
7. HASSAN W, OLDHAM R: Reiter's syndrome and reactive arthritis in health care workers after vaccination. *BMJ* 1994; 309: 94.
8. MAILLEFERT JF, SIBILIA J, TOUSSIROT E *et al.*: Rheumatic disorders developed after hepatitis B vaccination. *Rheumatology* 1999; 38: 978-83.
9. VAUTIER G, CARTY JE: Acute sero-positive rheumatoid arthritis occurring after hepatitis vaccination. *Br J Rheumatol* 1994; 33: 991.
10. GEIER MR, GEIER DA, ZAHALSKY AC: A review of hepatitis B vaccination. *Expert Opin Drug Saf* 2003; 2: 113-22.
11. POPE JE, STEVENS A, HOWSON W, BELL DA: The development of rheumatoid arthritis after recombinant hepatitis B vaccination. *J Rheumatol* 1998; 25: 1687-93.
12. TUDELA P, MARTI S, BONAL J: Systemic lupus erythematosus and vaccination against

hepatitis B. *Nephron* 1992; 62: 236.
13. GUISERIX J: Systemic lupus erythematosus following hepatitis B vaccine. *Nephron* 1996; 74: 441.
14. ALBITAR S, BOURGEON B, GENIN R *et al.*: Bilateral retrobulbar optic neuritis with hepatitis B vaccination. *Nephrol Dial Transplant* 1997; 12: 2169-70.
15. STEWART O, CHANG B, BRADBURY J: Simultaneous administration of hepatitis B and polio vaccines associated with bilateral optic neuritis. *Br J Ophthalmol* 1999; 83: 1200-1.
16. SINDERN E, SCHRODER JM, KRISMANN M, MALIN JP: Inflammatory polyradiculoneuropathy with spinal cord involvement and lethal outcome after hepatitis B vaccination. *J Neurol Sci* 2001; 186: 81-5.
17. VITALC,VITALA,GBIKPI-BENISSAN G *et al.*: Postvaccinal inflammatory neuropathy: peripheral nerve biopsy in 3 cases. *J Peripher Nerv Syst* 2002; 7: 163-7.
18. SINSAWAIWONG S, THAMPANITCHAWONG P: Guillain-Barre' syndrome following recombinant hepatitis B vaccine and literature review. *J Med Assoc Thai* 2000; 83: 1124-6.
19. CREANGE A, TEMAM G, LEFAUCHEUR JP: Lumbosacral acute demyelinating polyneuropathy following hepatitis B vaccination. *Autoimmunity* 1999; 30: 143-6.
20. TUOHYPG: Guillain-Barre syndrome following immunization with synthetic hepatitis B vaccine. *NZ Med J* 1989; 102: 114-5.
21. CARMELI Y, OREN R: Hepatitis B vaccine side-effect. *Lancet* 1993; 341: 250-1.
22. MACARIO F, FREITAS L, CORREIA J, CAMPOS M, MARQUES A: Nephrotic syndrome after recombinant hepatitis B vaccine. *Clin Nephrol* 1995; 43: 349.
23. ISLEK I, CENGIZ K, CAKIR M, KUCUKODUK S: Nephrotic syndrome following hepatitis B vaccination. *Pediatr Nephrol* 2000; 14: 89-90.
24. POULLIN P, GABRIEL B: Thrombocytopenic purpura after recombinant hepatitis B vaccine. *Lancet* 1994; 344: 1293.
25. VIALLARD JF, BOIRON JM, PARRENS M *et al.*: Severe pancytopenia triggered by recombinant hepatitis B vaccine. *Br J Haematol* 2000; 110: 230-3.
26. NEAU D, BONNET F, MICHAUD M *et al.*: Immune thrombocytopenic purpura after recombinant hepatitis B vaccine: retrospective study of seven cases. *Scand J Infect Dis* 1998; 30: 115-8.
27. TARTAGLINO LM, HEIMAN-PATTERSON T, FRIEDMAN DP,FLANDERS AE: MR imaging in a case of post vaccination myelitis. *Am J Neuroradiol* 1995; 16: 581-2.
28. TREVISANI F, GATTINARA GC, CARACENI P *et al.*: Transverse myelitis following hepatitis B vaccination. *J Hepatol* 1993; 19: 317-8.
29. INIGUEZ C, MAURI JA, LARRODE P, LOPEZ DEL VAL J, JERICO I, MORALES F: Acute transverse myelitis secondary to hepatitis B vaccination. *Rev Neurol* 2000; 31: 430-2.
30. MAHASSIN F, ALGAYRES JP, VALMARY J *et al.*: Acute myelitis after vaccination against hepatitis B. *Presse Med* 1993; 22: 1997-8.
31. KARAALI-SAVRUN F, ALTINTAS A, SAIP S, SIVAA : Hepatitis B vaccine related-myelitis? *Eur J Neurol* 2001; 8: 711-5.
32. SONG HK, KIM HC, YUN YH: Acute myelitis after hepatitis B vaccination. *J Korean Med Sci* 1997; 12: 249-51.
33. MEYBOOM RH, FUCIK H, EDWARDS IR: Thrombocytopenia reported in association with hepatitis B and A vaccines. *Lancet* 1995; 345: 1638.
34. ZAAS A, SCHEEL P, VENBRUX A, HELLMANN DB: Larger artery vasculitis following recombinant hepatitis B vaccination: 2 cases. *J Rheumatol* 2001; 28: 1116-20.
35. KEYSER FD, NAEYAERT JM, HINDRYCKX P *et al.*: Immune-mediated pathology following hepatitis B vaccination. Two cases of polyarteritis nodosa and one case of pityriasis rosea-like drug eruption. *Clin Exp Rheumatol* 2000; 18: 81-5.
36. LE HELLO C, COHEN P, BOUSSER M, LETELLIER P, GUILLEVIN L: Suspected hepatitis B vaccination related vasculitis. *J Rheumatol* 1999; 26: 191-4.
37. PENNESI M, TORRE G, DEL SANTO M, SONZOGNI A: Glomerulonephritis after recombinant hepatitis B vaccine. *Pediatr Infect Dis* 2002; 21: 172-3.
38. KONSTANTINOU D, PASCHALIS C, MARAZIOTIS T, DIMOPOULOS P, BASSARIS H, SKOUTELIS A: Two episodes of leukoencephalitis associated with recombinant hepatitis B vaccination in a single patient. *CID* 2001; 33: 1772-3.
39. PANDE H, LACYBE, CROWELL MD: Inflammatory causes of gastroparesis: report of five cases. *Dig Dis Sci* 2002; 47: 2664-8.
40. HASSAN W, OLDHAM R: Reiter's syndrome and reactive arthritis in health care worked after vaccination. *BMJ* 1994; 309: 94-5.
41. MAILLEFERT JF, SIBILIAJ, TOUSSIROT E *et al.*: Rheuamtic diseases developed after hepatitis B vaccination. *Rheumatology* 1999; 38: 978-83.
42. TARTAGLINO LM, HEIMAN-PATTERSON T, FRIEDMAN DP, FLANDERS AE: MR imaging in a case of post-vaccination myelitis. *AJNR* 1995; 16: 581-2.
43. POPE JE, STEVENS A, HOWSON W, BELL DA: The development of rheumatoid arthritis after recombinant hepatitis B vaccination. *J Rheumatol* 1998; 25: 1687-93.
44. GUIS S, JATTEI JP, NICOLI F *et al.*: Identical twins with macrophagic myofasciitis: genetic susceptibility and triggering by aluminic vaccine adjuvants ? *Arthritis Rheum* 2002; 47: 543-5.
45. MCMAHON BJ, HELMINIAK C, WAINWRIGHT RB, BULKOW L, TRIMBLE BA, WAINWRIGHT K: Frequency of adverse reactions to hepatitis B vaccine in 43,618 persons. *Am J Med* 1992; 92: 254-6.
46. RIETSCHEL RL, ADAMS RM: Reactions to thimerosal in hepatitis B vaccines. *Dermatol Clin* 1990; 8: 161-4.
47. GEIER MR, GEIER DA: Hepatitis B vaccination safety. *Ann Pharmacother* 2002; 36: 370-4.
48. DESTEFANO F, VERSTRAETEN T, JACKSON LA *et al.*: Vaccinations and risk of central nervous system demyelinating diseases in adults. *Arch Neurol* 2003; 60: 504-9.
49. SHOENFELD Y, AHARON-MAOR A, SHERER Y: Vaccination as an additional player in the mosaic of autoimmunity. *Clin Exp Rheumatol* 2000; 18: 181-4.
50. PIRMOHAMED M, WINSTANLEY P: Hepatitis B vaccine and neurotoxicity. *Postgrad Med J* 1997; 73: 462-3.