Short Communication

Major adverse reactions to yeast-derived hepatitis B vaccines—a review

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Yeast-derived recombinant DNA hepatitis B vaccines usage became widely accepted since the early 1990s. Severe adverse events have been reported infrequently in adults and rarely in infants and children given hepatitis B vaccine in the ten years which have passed since the introduction of the vaccine. Some of the data were summarized in previous review articles. Our review of the literature revealed reports of serious adverse reactions which included immediate reactions (anaphylaxis and urticaria) as well as delayed reactions, including skin, rheumatic, vasculitic (including Systemic Lupus Erythematosus and glomerulonephritis), hematologic, ophthalmologic and neurologic reactions. These cases were summarized and a pathogenetic mechanism is offered.

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BACKGROUND

Yeast-derived recombinant DNA hepatitis B vaccines were developed in the mid-1980s. Initial clinical trials were performed in 1984, and by 1986 the first human vaccines manufactured by recombinant DNA technology were licensed for general use. The vaccine was shown to be safe, immunogenic and protective against hepatitis B virus (HBV) infection and clinical HBV disease. It was initially recommended for individuals at high risk for acquiring infection. However, the use of yeast-derived vaccine became widely accepted because of its safety and immunogenicity profile, as well as the fact that it was inexpensive to produce, thus allowing for a near unlimited supply of vaccine. Since the early 1990s, universal immunization of infants is recommended and practiced in the United States, Europe and Israel.

Major adverse events have been reported infrequently in adults and rarely in infants and children given hepatitis B vaccine in the ten years which have passed since the introduction of the vaccine. Some of the data were summarized in previous review articles3,5. Herein we review all the reports of major adverse reactions that have been published since the introduction of the recombinant yeast-derived hepatitis B vaccine. These cases were summarized and a pathogenetic mechanism is offered.

HISTORY OF VACCINE DEVELOPMENT AND USAGE

During the 1970s HBsAg, purified from the plasma of healthy HBV carriers, was used to develop several hepatitis B vaccines. These vaccines were composed of non-infectious 22 nm HBsAg particles purified by physicochemical methods. Studies of safety, immunogenicity and efficacy4 led to the licensure and the use of the first plasma-derived hepatitis B vaccine in 19825. In the mid-1980s, recombinant DNA technology was used to express HBsAg. Vaccines that used yeast as the expression vector were licensed and gradually replaced the plasma-derived vaccine. Recombivax-HB® manufactured by Merck Sharp and Dohme (MSD), was licensed in 1986; Engerix-B®, manufactured by SmithKline Biologicals (SKB) was licensed in 1989. Another recombinant vaccine, Gen Hevac B®, manufactured by the Pasteur Institute is licensed in France. After initial licensure in the United States, hepatitis B vaccine was recommended for adults and children at high risk of HBV infection. In 1991, after recognizing that this strategy is not enough to reduce the incidence of HBV infection, the Immunization Practices Advisory Committee (ACIP) of the Center for Disease Control (CDC) proposed an immunization strategy for the elimination of transmission of HBV in the United States which includes universal immunization of infants6. This policy was accepted in many countries in Europe.

CHARACTERISTICS OF RECOMBINANT HEPATITIS B VACCINE

Recombinant technology for hepatitis B vaccine involves the insertion of segments of the HBV genome...
which encode HBsAg into a plasmid in the common baker's yeast (Saccharomyces cerevisiae), thus allowing for the expression HBsAg. The recombinant vaccines in use in North America and Europe (Recombinavax-HB<sup>®</sup> or Engerix-B<sup>®</sup>) are composed of the S antigen, without the pre-S regions. The HBsAg in the vaccine is the 22 nm subvirion particle, composed of a non-glycosylated 226 amino acid polypeptide. The vaccine also contains yeast lipids, aluminum hydroxide as an adjuvant and thimerosal as a preservative.

The yeast cells are disrupted and the HBsAg is purified to the point where each lot of vaccine has only a trace amount of yeast-derived components. The Gen Hevac B<sup>®</sup> vaccine, which is manufactured by the Pasteur Institute, is a recombinant vaccine produced in mammalian cells, and contains the S and pre-S2 antigens.

SAFETY OF RECOMBINANT HEPATITIS B VACCINE

In the clinical trials with recombinant hepatitis B vaccines, the most frequent side effects reported were injection site soreness sometimes accompanied by erythema (3–29%), fatigue (15%), headache (9%) and a temperature greater than 37.7°C (1–6%)<sup>1</sup>. Other reported symptoms (such as gastrointestinal upset) seemed temporal and not causal. Review of the post-marketing surveillance literature (4.5 million doses) revealed an overall rate of one adverse effect per 15,500 doses distributed. Of these, local reactions were reported to be the only events unequivocally related to the vaccine (at a rate of 1 in 85,000 doses)<sup>2</sup>. These reactions included nausea, rash, headache, fever, malaise, injection site symptoms, fatigue, influenza like symptoms, vomiting, dizziness, pruritus, arthralgia, myalgia, diarrhea, urticaria, paraesthesia and somnolence all of which resolved, generally within 24–48 h of vaccine administration. Reactions were less frequent with subsequent doses. No serious or severe reactions attributable to the vaccines were reported. Since the publication of the above-mentioned surveillance (1990), some major adverse events have been reported. These include immediate reactions (anaphylaxis and urticaria) as well as delayed reactions, including skin, rheumatic, vasculitic (including systemic lupus erythematosus and glomerulonephritis), hematologic, ophthalmologic and neurologic reactions.

MAJOR ADVERSE EFFECTS OF RECOMBINANT HEPATITIS B VACCINE

Acute reactions

A causal relation was established in a case report of anaphylaxis submitted to the Vaccine Adverse Events Reporting System of the Institute of Medicine at the National Academy of Sciences, Washington, DC<sup>10</sup>. Acute urticaria of the neck and chest area was reported in a 24-year-old nurse 30 min after receiving the first dose of Engerix-B<sup>®</sup> vaccine. The patient had a history of recurrent idiopathic urticaria since the age of ten years. A year later, a thimerosal free plasma-derived vaccine was administered to the patient and resulted in throat itching and tightness, which ceased after receiving subcutaneous epinephrine. Skin test to both vaccines, baker's yeast, crude vaccine preparations of the Engerix-B<sup>®</sup> vaccine before the addition of thimerosal and aluminum and the preservative (phenol), were negative. Patch test was positive to thimerosal<sup>1</sup>.

Skin reactions

Erythema nodosum was described in a 43-year-old female patient four days after receiving the first dose of Recombinavax-HB<sup>®</sup> vaccine. Other causes of erythema nodosum were ruled out. She had a history of asthma, pulmonary interstitial fibrosis and eczema. Her chest film showed nonspecific chronic interstitial reticulonodular marking. Laboratory findings were normal except for an elevated IgE concentration (1387 IU ml<sup>−1</sup>), and a positive skin test to aspergillus antigen. The skin lesions disappeared gradually over several weeks but reappeared three days after re-challenge with another dose of vaccine<sup>2</sup>. Another case of Erythema nodosum and polyarthritus was reported and will be described in the rheumatic reactions section. Lichen planus was described in two case reports. The first was a 19-year-old woman two months after receiving the second dose of Recombinavax-HB<sup>®</sup> vaccine<sup>3</sup>. The second was a 30-year-old man one month after the second dose of Gen Hevac B<sup>®</sup> vaccine. Treatment with systemic corticosteroids and psoralen plus UV-A cleared the eruption within three months<sup>4</sup>. In both cases the histologic features of the skin lesions were typical of lichen planus. Another young woman developed lichen planus after receiving the plasma derived hepatitis B vaccine<sup>5</sup>.

Rheumatic reactions

Arthritis was described in few patients after receiving hepatitis B vaccine. Most of them were related to the plasma derived vaccines<sup>6</sup>, but in 1989 a case of polyarthritus and erythema nodosum was reported in a 31-year-old man after the first dose of Engerix-B<sup>®</sup>. One day after receiving the vaccine he developed polyarthritus involving small and large joints and skin lesions which were consistent in appearance with erythema nodosum. He had no history of arthritis, eye or chest disease. The skin reaction lasted for one week, but the arthritis persisted for six weeks and was initially severely incapacitating. The patient was unwilling to receive further vaccination<sup>7</sup>. Joint complaints also occurred in a 41-year-old female nurse who developed migratory arthritis two weeks after receiving a single dose of the vaccine<sup>8</sup>. The symptoms lasted for seven months, during which she was treated with nonsteroidal anti-inflammatory drugs (NSAID). She was observed for a further six months without recurrence. Reiter syndrome in association with Engerix-B<sup>®</sup> vaccine was described in a 29-year-old health care worker who developed polyarthritus four weeks after the second injection of the vaccine. He also developed bilateral conjunctivitis and dysuria. Urine cultures were sterile for six months, although he suffered from intermittent dysuria during that time. He was treated with NSAID, but received steroids after developing persistent swelling of the knees and wrists. His symptoms improved gradually over the next four months, drugs were withdrawn, and there was no recurrence over the following year<sup>9</sup>. Rheumatoid arthritis
Vasculitis

Pulmonary and cutaneous vasculitis was described in a 45-year-old previously healthy woman. Two days after the first dose of Engerix-B® was administered, she developed a pruritic, maculopapular rash over most of her body. She also developed dyspnea on minimal exertion, signs of peripheral vasculitis, and polyarthritis. Investigations showed signs of probable pulmonary vasculitis (basilar basal mottling on chest radiograph and restrictive pattern in pulmonary function tests), and cutaneous vasculitis (confirmed by skin biopsy). Serology for antinuclear factor, rheumatoid factor and cold agglutinins were negative and complement levels were normal. There was no laboratory evidence of viral or Mycoplasma infection. Treatment with steroids produced a rapid clinical response with resolution of the rash, arthralgia and the radiographic abnormalities. She remained free of disease over a period of 12 months.

Systemic lupus erythematosus (SLE)

A 43-year-old woman received a first dose of Engerix-B® and two weeks later, edema of both legs was developed. Four weeks later she was first evaluated, and the laboratory tests were consistent with SLE with renal involvement. The patient was treated with steroids and cyclophosphamide with favorable results.

Glomerulonephritis was described in a 21-year-old man six weeks after a third dose of Engerix-B®. Laboratory investigations failed to reveal evidence of rheumatologic or infectious disease. In a few days most of his signs resolved completely, without treatment.

Hematologic reactions

Evans’ syndrome was reported in a 33-year-old man two days after receiving a second dose of Engerix-B® vaccine. He presented with acute abdominal pain, polyarthritis affecting hands and feet, chills and fever. Laboratory examinations diagnosed acute autoimmune hemolytic anemia (positive direct Coombs’ test for IgG and C3) and thrombocytopenia (with circulating immune complexes and IgG platelet-bound antibodies). Infectious causes such as cytomegalovirus, Epstein-Barr virus, hepatitis A, B and C viruses, syphilis, HIV, Mycoplasma pneumoniae and toxoplasma were ruled out. Tests for rheumatoid factor, anti-smooth muscle, anti-gastric mucosa, antimitochondrial and antithyroid antibodies were negative. He was treated with steroids and the clinical signs and laboratory abnormalities resolved over two months. After six months follow-up, the patient was asymptomatic, with a normal hemoglobin and platelet count. Thrombocytopenic purpura was described in two young women in association with hepatitis B vaccine. The first was a 15-year-old girl with purpura four weeks after receiving a third dose of hepatitis B vaccine (Gen Hvac B®). The second was a 21-year-old nurse with purpura and splenomegaly three weeks after a second dose of Engerix-B®. In both cases, thrombocytopenia was detected and the diagnosis of immune-mediated disease was confirmed by detecting IgG platelet-bound antibodies. The first patient was treated successfully with a four-month course of steroids and intravenous immunoglobulin, while the second patient remained thrombocytopenic despite two months of steroid therapy.

Ophthalmologic reactions

Two cases of acute posterior multifocal placoid pigment epitheliopathy (APMPPE) were described. The first was a 31-year-old man following a booster vaccination of yeast derived hepatitis B vaccine (Engerix-B®). The patient received three doses of plasma-derived hepatitis B vaccine 33, 32 and 31 months previously. Three days after vaccination he developed a visual loss in the right eye. Visual acuity was 20/200 (OD) and 20/20 (OS). Funduscopy examination and fluorescein angiography showed multiple lesions in the retinal pigment epithelium in the macular area. Four days later, vision improved to 20/80 OD, but pigment clumping was seen in the right fovea and temporarily in the fovea of the left eye. The only laboratory abnormality detected was eosinophilia of 24%. Over nine months follow-up, vision improved to 20/25 OD, with a central scotoma; a left temporal scotoma was also detected. His Eosinophil count decreased after three months. A second case of APMPPE was described in a 30-year-old man two weeks after a third dose of Engerix-B® vaccine. No adverse effects were recognized after the first two doses of the same vaccine. Visual acuity was 20/20 OD and 20/200 OS. Funduscopy examination revealed multiple pale lesions in both eyes. Two months after vaccination, fluorescein angiography showed retinal pigment epithelium scarring in both eyes, with a left predominance. After a four month follow-up, visual acuity improved to 20/30 OS, although there was a residual paracentral scotoma.

Neurologic reactions: demyelinating disease of the central nervous system (CNS)

Guillain-Barré syndrome27 and transverse myelitis28 have been reported after administration of plasma-derived hepatitis B vaccines. The first neurologic adverse reaction following yeast-derived hepatitis B vaccine was a case of Guillain-Barré syndrome, which was reported by the WHO Drug Information27. Since then few cases of CNS demyelination after immunization with recombinant hepatitis B vaccine were published29. The first was a 26-year-old health-care worker who had a history of relapsing–remitting multiple sclerosis, with good recovery. Six weeks after receiving a third dose of Engerix-B® vaccine, she...
reported left-sided hemiparesis with impaired sensa-
tion. Treatment with intravenous steroids led to partial
improvement. Two weeks later she was re-admitted
with left-sided hemiplegia and became comatose.
Steroids and mannitol were given, with substantial
improvement over the next few days. Left-sided
hemiparesis persisted, but there have been no further
relapses during the next four years. The second was a
28-year-old nurse, who was given a second dose of
Engerix-B®. Six weeks later, she developed right
inferior homonymous quadrantanopia and paresis of
the right arm and leg, with diminished sensation in the
right leg. Steroids were given intravenously with slight
improvement in muscle strength. One month later
severe right hemiparesis occurred, with dense right
homonymous hemianopia. Three months later, she still
had a spastic right-sided hemiparesis and incomplete
right homonymous hemianopia. A case of acute trans-
verse myelitis occurred in a 40-year-old health care
worker. Symptoms began two weeks after receiving
the first dose of recombinant hepatitis B vaccine and
included lower-extremity numbness and walking diffi-
culty, with progression after the administration of the
second dose of the vaccine. The patient presented six
weeks after onset of symptoms with markedly impaired
proprioception and vibration sense, minimal weakness,
hyporeflexia in the lower extremities and a T-4 sensory
level. Magnetic resonance findings were consistent with
that of transverse myelitis and with residual posterior
column dysfunction. A case of multiple sclerosis after
hepatitis B vaccination was described in a 43-year-old
industrial chemist involved in assays of waste, who
received a dose of Engerix-B®. Seven to 10 days later
she developed fever, ache, gastric upset and tingling of
her right fingers and toes. These symptoms progressed
over three weeks to right hemiparesis with decreased
sensation, numbness of the right side of the tongue,
and dysdiadochokinesis. Her medical and family history
were noncontributory, and there were no epidemi-
ological, clinical or laboratory signs of an infectious
disease. The patient was given a trial of therapy with
ACTH, but the response was minimal. She developed
swallowing and speech difficulties, a right facial droop,
ocular nystagmus, spastic gait, and bilateral ankle
clonus. Five months later, she still had difficulties in
swallowing, sitting, writing, and ambulating. A case of
acute cerebellar ataxia was described in a 26-year-old
woman (a medical-technical assistant) ten days after a
second dose of Engerix-B®. She developed ataxia of
gait which reached its climax ten days later. Her neuro-
ological examination showed a cerebellar as well as
pyramidal tract disturbance. Laboratory tests, antibody
titters for an acute infectious disease, ECG, X-rays,
CT-scans and MRI were normal. After two weeks her
ataxia began to improve slowly, without any treatment.
Four months after onset of the disease, the patient
recovered.

**Chronic fatigue syndrome (CFS)**

In Canada, 30 self-reported cases of CFS (meeting a
standard case definition) alleged to be secondary to
hepatitis B vaccination. A working group on that
possible association agreed that there is no evidence of
a cause–effect relationship between hepatitis B vaccin-
ation and CFS. Table 1 summarizes all 21 reported cases of major
adverse reactions after recombinant hepatitis B vaccin-
ation, according to the gender and the age of the
vaccine recipient, the dose number, the time after
vaccination, symptom duration and relevant clinical
background.

### Table 1  Summary of important adverse reactions after recombinant hepatitis B vaccination

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Sex</th>
<th>Age</th>
<th>Dose</th>
<th>Time after vaccination</th>
<th>Duration of symptoms</th>
<th>Clinical background</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute urticaria</td>
<td>F</td>
<td>24</td>
<td>1</td>
<td>30 minutes</td>
<td>30 minutes</td>
<td>Rec. idiopathic urticaria</td>
<td>11</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>F</td>
<td>45</td>
<td>1</td>
<td>4 days</td>
<td>Several weeks</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Lichen planus -1</td>
<td>F</td>
<td>19</td>
<td>2</td>
<td>2 months</td>
<td>Not reported</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Lichen planus -2</td>
<td>M</td>
<td>50</td>
<td>2</td>
<td>1 month</td>
<td>3 months</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Polyarthritis (1) +</td>
<td>M</td>
<td>31</td>
<td>1</td>
<td>1 day</td>
<td>6 weeks</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyarthritis - 2</td>
<td>F</td>
<td>41</td>
<td>2</td>
<td>2 weeks</td>
<td>7 months</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Reiter Syndrome</td>
<td>M</td>
<td>29</td>
<td>2</td>
<td>4 weeks</td>
<td>4 months</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>F</td>
<td>49</td>
<td>1</td>
<td>24 hours</td>
<td>Not reported</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Pulmonary and systemic vasculitis</td>
<td>F</td>
<td>45</td>
<td>1</td>
<td>2 days</td>
<td>1 week</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>F</td>
<td>43</td>
<td>1</td>
<td>2 weeks</td>
<td>Not reported</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>M</td>
<td>21</td>
<td>6</td>
<td>6 weeks</td>
<td>Few days</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>Evand’s syndrome</td>
<td>M</td>
<td>30</td>
<td>3</td>
<td>3 days</td>
<td>2 months</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Thrombocytopenic purpura -1</td>
<td>F</td>
<td>15</td>
<td>1</td>
<td>4 weeks</td>
<td>4 months</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Thrombocytopenic purpura - 2</td>
<td>F</td>
<td>21</td>
<td>3</td>
<td>3 weeks</td>
<td>2 months at least</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Acute posterior multiscleral plaicid</td>
<td>F</td>
<td>31</td>
<td>4</td>
<td>3 days</td>
<td>9 months (residual signs)</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>pigment epitheliopathy - 1</td>
<td>M</td>
<td>30</td>
<td>3</td>
<td>2 weeks</td>
<td>4 months (residual signs)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Acute posterior multiscleral plaicid</td>
<td>M</td>
<td>30</td>
<td>3</td>
<td>2 weeks</td>
<td>4 months (residual signs)</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Central nervous system demalination-1</td>
<td>F</td>
<td>26</td>
<td>6</td>
<td>6 weeks</td>
<td>3 weeks (residual signs)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Central nervous system demalination-2</td>
<td>F</td>
<td>28</td>
<td>1</td>
<td>6 weeks</td>
<td>6 weeks (residual signs)</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Acute transverse myelitis</td>
<td>M</td>
<td>40</td>
<td>1</td>
<td>2 weeks</td>
<td>6 weeks (residual signs)</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>F</td>
<td>43</td>
<td>1</td>
<td>7-10 days</td>
<td>4 months</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>Acute cerebellar ataxia</td>
<td>F</td>
<td>26</td>
<td>2</td>
<td>10 days</td>
<td>4 months</td>
<td></td>
<td>34</td>
</tr>
<tr>
<td>Median</td>
<td>a</td>
<td>31</td>
<td>14</td>
<td>14 days</td>
<td>8 weeks</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Average</td>
<td>a</td>
<td>32</td>
<td>19</td>
<td>19 days</td>
<td>11 weeks</td>
<td></td>
<td>36</td>
</tr>
</tbody>
</table>

**Notes:**

- Male/female ratio = 8/13, nine patients developed reactions after first dose, 12 developed reactions after more than one dose
- Calculations for neurologic reactions are based on the minimal period mentioned in the case reports
- Acute urticaria and all cases in which symptoms' duration was not reported are not included in these calculations
DISCUSSION

Apart from one case of possible anaphylaxis, and one case of urticaria and asthma, most of the reactions described were not allergic in nature and the symptoms are those of immune complex disease. Auto-immune mechanisms have been implicated in all the following: SLE, erythema nodosum, rheumatoid arthritis, glomerulonephritis, Reiter syndrome, Evans' syndrome, thrombocytopenic purpura, multiple sclerosis, and vasculitis. Guillian-Barré syndrome and APMPPE are possibly immune complex diseases; most cases of acute cerebellar ataxia occur in association with infectious diseases while few cases after DTP and influenza vaccination. This may also suggest an immune-complex mechanism. The formation and deposition of immune complexes with complement activation is a major pathogenic mechanism in the development of all these adverse reactions in several infectious and systemic diseases, including hepatitis B infection.

The link between the adverse effects described, immune-complex disease and hepatitis B vaccine can be explained in three ways. First, that it is coincidental. Second, that the patient developed a post-immunization disease, clinically indistinguishable from the natural form of the disease. Finally, that the patient had a pre-existing immunological susceptibility, which after the antigenic stimulus of hepatitis B recombinant surface vaccine, triggered the pathologic process that led to clinical disease.

Because of the extreme rarity of serious adverse effects, coincidence seems the simplest explanation, but similar reactions have also been described in hepatitis B infection, and may share an immune complex mediated pathogenesis. Given that recombinant hepatitis B vaccines contain only S-antigen, it is highly unlikely that this protein could cause active disease in the absence of the host's response. Although a causal association between vaccination and adverse effects has not been proven, it appears to be strongly supported both by a close temporal relationship between vaccination and the onset of the symptoms, and by the immune-mediated nature of these manifestations. Furthermore, in most cases, most other etiologies associated with these phenomena other than hepatitis B, were excluded.

Immune complexes containing HBsAg have been detected in the sera and tissues of patients with acute and chronic hepatitis B, and in asymptomatic carriers. Immune complex disease similar to serum sickness, leading to extrahepatic manifestations, has been described in hepatitis B infected subjects. These manifestations include glomerulonephritis, membranous nephropathy, arthritis, polyarthritis nodosa, erythema multiforme, erythema nodosum, uveitis and Guillian-Barré syndrome. These manifestations are associated with the prodromal phase of acute hepatitis B and usually last a few days. Laboratory findings during this phase include decreased C3 and C4 levels, and circulating cryocomplexes, suggesting that activation of the complement system by immune complexes is the mechanism by which extrahepatic manifestations associated with hepatitis B infection occur.

Administration of hepatitis B vaccine may lead to the simultaneous presence of a large amount of antigen and small amounts of antibodies in the serum (similar to that seen in the prodromal phase of hepatitis B infection), and may, in turn, induce the formation of soluble antigen–antibody complexes, thus initiating clinical disease. In order to establish the immune mediated nature of these phenomena, immune complexes containing HBsAg and antibodies must be identified in sera or tissue of recently vaccinated individuals with immune complex manifestations.

The third explanation, which claims that the patients had a specific underlying immunological susceptibility to HBsAg or other vaccine component, can be supported by evidence which suggest that the administration of various vaccines may precipitate clinical manifestations of autoimmune disease. Other vaccines, such as BCG or influenza vaccine, have been reported to induce deterioration in the clinical state of patients with SLE. Perhaps these immunizations stimulate an increase in the number of circulating immune complexes. This phenomenon is poorly-tolerated in these patients since their capacity to clear such products is decreased. On the other hand, in ten years surveillance for post-vaccination neurological symptoms consistent with Encephalomyelitis disseminata, no increase in the frequency of initial or renewed attacks following immunization was noted.

Apart from the immune complex mechanism, there are some other ways by which hepatitis B vaccine could cause severe adverse effects. Reactions may occur because of the minute quantities of yeast proteins present in the vaccine. The potential of these proteins to induce a hypersensitivity reaction in primed individuals was examined by measuring of IgG and IgE antibody to yeast before and after three doses of vaccine. No significant increases occurred in most individuals and in those who experienced increases there was no correlation with clinical symptoms. Other components of hepatitis B vaccine, such as thimerosal and aluminum, have been implicated in hypersensitivity reactions. Confirmed hypersensitivity to thimerosal was demonstrated in the patient who developed urticaria and asthma after hepatitis B vaccination. Inflammatory nodular reactions after hepatitis B vaccination due to aluminum sensitization were reported in two patients. These hypersensitivity responses cannot explain most of the post vaccination adverse effects described, which, as mentioned above, were mostly non-allergic in nature. In addition, some of the reported adverse effects seen after administration of recombinant, yeast-derived vaccine, were described also after patients received the plasma-derived vaccine. This probably excludes the role of yeast or other non-surface antigen recombinant vaccine component in these reactions.

Molecular mimicry should also be taken into consideration as a possible pathogenic pathway, especially for the rheumatic reactions. Cross-reacting determinants between some infectious antigens and the host have been found, e.g. HLA B-27 and Yersinia or Klebsiella and DR4 or DR2 and Group A beta-hemolytic Streptococcal antigens. This is possible regarding HBsAg as well.

In conclusion, the similarity between serious adverse reactions to hepatitis B vaccine and the extrahepatic manifestations of hepatitis B infection, their temporal relationship to hepatitis B vaccination, and the possible...
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immune complex mechanism suggest a possible etiologic link with hepatitis B vaccine. These effects are very rare, and may, in part, be immune mediated.

In view of the campaigns for universal hepatitis B vaccination in some countries, the appearance or exacerbation of auto-immune disease may become more frequent and should be actively sought and reported. Caution should be used in the management of a patient with a history of an allergic-type reaction to this vaccine. Once a serious adverse event occurred, the patient should not undergo further vaccinations. Although a causal relationship between vaccination and the adverse effects reported is not proven, recombinant hepatitis B vaccination should be considered with caution in patients with known auto-immune disease. The preventive benefits of hepatitis B vaccination for the general population still far outweigh the potential risks.

REFERENCES


8. CDC. Update: Vaccine side effects, adverse reactions, contraindications and precautions. MMWR 1996, 45, 1–35.


