

# No Evidence of Autoimmunity in 6-Year-Old Children Immunized at Birth With Recombinant Hepatitis B Vaccine

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**ABSTRACT.** *Objectives.* Taking into account that genetic predisposition, marked by human leukocyte antigen (HLA) class I and II genes, augments the probability of developing an autoimmune disorder after a triggering vaccination, as largely debated, we investigated the frequency of autoantibody production after recombinant hepatitis B vaccine (rHBv) in 6-year-old children immunized at birth to evaluate an association between autoimmune disorders and hepatitis B virus vaccination.

*Methods.* We investigated the presence of autoantibodies in 210 6-year-old children who were immunized at birth with rHBv: 200 showed anti-hepatitis B surface antigen concentrations  $\geq 10$  mUI/mL at seroconversion (responders), and 10 were nonresponders. Data were compared with those obtained in 109 unvaccinated children. All participants were screened for the presence of antinuclear antibodies (ANAs), anti-DNA, antimitochondrial, anti-liver/kidney microsomal, antireticulin, anti-smooth muscle (SMA), and antiribosomal antibodies. All participants were also screened for the presence of antithyroid antibodies, such as antithyroglobulin and antiperoxidase, and for antibodies found in type 1 diabetes, such as tyrosine phosphatase (IA-2A) and glutamic acid decarboxylase (GADA). HLA typing was extended to all 10 nonresponders.

*Results.* Autoantibodies were found in 16 of the 200 responders: ANAs were found in 12 (6%), smooth muscle antibodies were found in 4 (2.0%), and antireticulin antibodies and endomysial antibodies were found in 1 girl with ANAs. Antithyroid antibodies, IA-2A, and GADA were not present in any of the participants. No significant difference was found in the frequency of autoantibodies between vaccinated and control children. Three of the 10 nonresponder children were SMA-positive (30% vs 2% of responders); they also carried the supertype HLA-C4A\*Q0,DRB1\*0301,DQB1\*02. A family history for autoimmune disorders was present in 3 (18%; 95% confidence interval [CI]: 4.0%–45.6%) of the 16 responder

infants with autoantibodies, in 15 (8.4%; 95% CI: 4.6%–13.1%) of responder children without autoantibodies, and in 1 (10%) of the 10 nonresponder children.

*Conclusions.* From our data, vaccination with rHBv given during the neonatal period does not seem to increase autoantibody production in a 6-year-old children. Autoantibodies, referred to as natural autoantibodies, can be found in healthy participants, but their significance is unclear. These autoantibodies often cross-react with bacteria or tumor antigens, suggesting their importance in innate immunity. It has been demonstrated in an animal model that self-antigen can promote B-cell accumulation, and that a significant proportion of natural autoantibodies is the product of this self-antigen-dependent process. Consequently, it has been speculated that self-antigens play a positive role in recruiting B cells as a part of innate immunity, but this process carries a potential risk for unregulated growth.

Spreading of the immune response is a common theme in organ-specific and systemic autoimmune diseases, and this could be initiated by exogenous agents, in genetically susceptible hosts, owing to molecular mimicry of natural antigen. Moreover, 3 (18%) of the 16 children who had autoantibodies had a family history of autoimmune diseases. Thus, it is apparent that susceptibility to autoimmunity is determined by genetic factors rather than by vaccine challenge. Among all the children considered, only 1 girl (0.5%) developed celiac disease, reflecting the prevalence described in the literature. GADA and IA-2A were not found in our children; this observation is in agreement with data showing that type 1 diabetes risk may not be altered by vaccinations administered during childhood. On the contrary, a high frequency (30%) of autoantibodies, in particular SMA, was observed in the nonresponder children. The 3 SMA-positive children carried the HLA-C4A\*Q0,DRB1\*0301,DQB1\*02 haplotype, a well-known predisposing factor for autoimmune disorders. On the other hand, the presence of autoantibodies to smooth muscle is known to be common in hepatitis B infection, and, it has been shown that cross-reactive immunity targeting homologous self-protein may partly account for autoantibody production. Although hepatitis B vaccination given during the neonatal period does not increase autoantibody production in 6-year-old immunized children, we deem useful a more prolonged follow-up for these nonresponder children carrying certain HLA haplotypes (such as C4A\*Q0,DRB1\*0301,DQB1\*02), particularly because most autoimmune diseases do not develop until later in life. *Pediatrics* 2002;110(1). URL: <http://www.pediatrics.org/cgi/content/full/110/1/e4>; *hepatitis B vaccine, autoantibody, autoimmune diseases.*

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ABBREVIATIONS. HLA, human leukocyte antigen; rHBv, recombinant hepatitis B vaccine; HBsAg, hepatitis B surface antigen; SR,

slow responder; TNR, true nonresponder; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; GADA, glutamic acid decarboxylase antibodies.

Several autoimmune disorders have been described after vaccination procedures.<sup>1-3</sup> Molecular mimicry has been suggested as a possible pathogenetic mechanism.<sup>1,4</sup> The evidence regarding the relationship between vaccination and autoimmune diseases is controversial; nevertheless, some autoimmune phenomena clearly seem to be related to immunization (eg, Guillain-Barré syndrome).<sup>5</sup> In animal models, it is apparent that commonly given vaccines induce a variety of autoantibodies but no frank autoimmune illness.<sup>6</sup> In genetically predisposed animals, though, it has been reported that immunization with cytomegalovirus glycoprotein gB can trigger the development or acceleration of an autoimmune disorder.<sup>7</sup> In humans, it has been reported that natural infection or vaccination against measles and/or mumps could have an inhibitory effect on the development of thyroid autoantibodies, but no evidence was found that measles, mumps, and rubella vaccination might trigger autoimmunity.<sup>8</sup> Vaccinations against hepatitis B, tetanus, or influenza do not seem to increase the onset or lead to relapses in multiple sclerosis.<sup>9,10</sup>

The presence of autoantibodies is associated with autoimmune diseases<sup>11</sup>; nevertheless, it has been reported that healthy children could transiently present autoantibodies (natural autoantibodies).<sup>12</sup> However, genetic predisposition, marked by human leukocyte antigen (HLA) class I and II genes, augments the probability of developing an autoimmune disorder after a triggering vaccination.<sup>1</sup> In a previous study, conducted on children who were immunized at birth with recombinant hepatitis B vaccine (rHBv), we demonstrated that different HLA products seem to act as agonists (C4A\*0, DRB1\*0301, and DQB1\*02) or antagonists (DRB1\*11 and DQB1\*0301) in lowering humoral response to rHBv.<sup>13</sup> Because HLA-DRB1\*0301, DQB1\*02, and C4A\*0 are markers of autoimmune diseases, these results suggest that non-responsiveness to hepatitis B virus peptides might identify participants with a genetic risk of developing autoimmune pathologies.

The aim of the present study was to define the frequency of autoantibody production after rHBv in 6-year-old children who were vaccinated at birth.

## METHODS

### Study Population

We evaluated the presence of autoantibodies in 210 6-year-old children who were vaccinated at birth with rHBv. Written informed consent was obtained from guardians. The study population included the following cohorts:

- Two hundred children (91 boys and 109 girls) recruited from a group of 408 born to anti-hepatitis B surface antigen (HBsAg)-negative mothers between May 1 and December 31, 1991, and showing anti-HBsAg concentrations  $\geq 10$  mIU/mL at seroconversion. Eighty-three of these infants received 10  $\mu$ g of rHBv intramuscularly on the fourth day, at 1 month, and at 3 months of life (accelerated schedule); the other 117 infants received 10  $\mu$ g of rHBv intramuscularly on the fourth day, at 1 month, and 6 months of life (traditional schedule). Anti-HBsAg concentra-

tion was evaluated 30  $\pm$  7 days after the last dose of vaccine (seroconversion).<sup>14</sup>

- Ten children enrolled from a cohort of 184 of 4835 newborns vaccinated at birth from January 1992 to March 1998, selected for being rHBv nonresponders (anti-HBsAg levels  $< 10$  mIU/mL at seroconversion) and 6 years old.

Serum samples of all the enrolled participants were collected and stored at  $-80^{\circ}\text{C}$  until analysis, performed at the same time.

All 4835 participants had received 3 doses of 10  $\mu$ g of Engerix B recombinant vaccine at 4 days, 1 month, and 6 months of age. The anti-HBsAg concentration was evaluated 30  $\pm$  7 days after the last dose of vaccine.

Infants with antibody level  $< 10$  mIU/mL at seroconversion were boosted with an additional dose of vaccine. Three classes of participants were identified, as reported elsewhere<sup>13</sup>:

- Responders, if they had antibody level  $\geq 10$  mIU/mL at seroconversion.
- Slow responders (SRs), if they had antibody levels  $< 10$  mIU/mL at the time of seroconversion but  $> 10$  mIU/mL after the booster dose of vaccine.
- True nonresponders (TNRs), if they had antibody levels steadily  $< 10$  mIU/mL also after the booster dose of vaccine.

Of the 10 nonresponder children included in this study, 8 were TNRs and 2 were SRs.

In the 200 responding and 10 nonresponding participants enrolled, family history for autoimmune diseases was investigated through a structured questionnaire. Data observed in responder and nonresponder children were compared with those obtained in a historical control group of 109 participants (75 boys and 34 girls; age range: 2-6 years; mean age: 5.1 years) who had not been vaccinated against hepatitis B because they were born before anti-hepatitis B virus immunization became mandatory for newborn children.<sup>12</sup> This sample had a statistically significant difference in gender composition with respect of immunized sample.

### Anti-HBsAg Antibody Levels

Anti-HBsAg antibody levels were evaluated by an enzyme immunoassay (AUSB EIA kit; Abbott Laboratories, Chicago, IL). The limit of detection was 0.1 mIU/mL. Levels  $\geq 10$  mIU/mL were considered protective.

### Non-Organ-Specific Autoantibodies

All participants were screened in the same time for the presence of antinuclear (ANA), anti-DNA, antimitochondrial, anti-liver/kidney microsomal, antireticulin, anti-smooth muscle (SMA), and antiribosomal antibodies by immunofluorescence on cryostat section of rat liver and kidney as antigen. Sera were diluted 1:10, and fluorescein-conjugated rabbit anti-human immunoglobulin (Dako, Copenhagen, Denmark) was used as previously described.<sup>12</sup> Results were expressed as negative (-), positive (+), and strongly positive (++) .

### Organ-Specific Autoantibodies

All participants were screened in the same time for the presence of antithyroid antibodies such as antithyroglobulin and antiperoxidase by radioimmunoassay (CIS Bio International, Cedex, France). With regard to type 1 diabetes, the measurement of autoantibodies to tyrosine phosphatase (IA-2) and to glutamic acid decarboxylase was determined by radioimmunoassay (CIS Bio International). Glutamic acid decarboxylase antibodies (GADA) levels  $> 0.9$  and IA-2A levels  $> 0.75$  were considered positive. Inter- and intra-assay coefficient of variation was 7.2% and 2.9%, respectively.<sup>15</sup> With regard to celiac disease, antendomysial antibodies were determined by immunofluorescence (Bios GmbH, Graefelfing, Germany) on cryostat section of distal monkey esophagus.<sup>16</sup> The person who performed the test was blinded to the cohort under examination.

### HLA Typing

HLA class I and II genomic polymorphism at high-resolution level was defined in all of the nonresponder children. HLA class III typing for C4A and C4B was performed at the protein level, as previously described.<sup>13</sup>

## Statistical Analysis

Autoantibody frequencies in all groups were compared by means of  $\chi^2$  or Fisher exact test, as appropriate.  $P < .05$  was considered significant.

## RESULTS

As shown in Table 1, autoantibodies were detected in 16 of 200 responders (8%) according to the following distribution: ANA in 12 participants (6%), SMA in 4 (2.0%), and antireticulin antibodies and endomy-sial antibodies in 1 girl with ANA. An intestinal biopsy performed in this girl confirmed the diagnosis of celiac disease. Antithyroid antibodies were not detected, and anti- $\beta$ -cell autoantibodies (IA-2A and GADA) were lower than cutoff values in all participants. Autoantibodies were detected in 5 of 83 children (6%) who received the accelerated schedule and in 11 of 117 children (9.4%) who received the traditional immunization schedule; the difference was not significant. Comparisons between the single autoantibody frequencies in the 2 schedules also were not significant. Because there were no differences in autoantibody production between the 2 groups, we considered the population as homogeneous, and all additional analyses were performed on the entire group. Autoantibodies were detected in 16 of 200 vaccinated children (8%) and in 10 of 109 children (9.4%) who were not immunized with rHBV; the difference was not statistically significant. Comparisons between the single autoantibody frequencies in the 2 groups also were not significant.

Of the 10 nonresponder children, 2 TNRs and 1 SR were SMA positive (Table 2); the 3 SMA-positive children were C4AQ0, DRB1\*0301, and DQB1\*02 positive. The difference in SMA production between the responder group (2%) and the TNR/SR cohort (30%) was statistically significant ( $P = .0025$ ).

A family history for autoimmune disorders was present in 3 of the 16 responder infants with autoantibodies (18%; 95% confidence interval: 4.0%–45.6%), in 15 responder children without autoantibodies (8.4%; 95% confidence interval: 4.6%–13.1%), and in 1 of the 10 nonresponder children (10%).

## DISCUSSION

From our data, vaccination with rHBV given in neonatal age does not seem to increase autoantibody

**TABLE 1.** Autoantibody Prevalence in 200 Responder Children 6 Years After Anti-HBV Immunization and in 109 Unvaccinated Infants (Controls)

NOSA	Immunized Children ( $n = 200$ )		Controls ( $n = 109$ )
	Accelerated Schedule ( $n = 83$ )	Traditional Schedule ( $n = 117$ )	
ANA	4 (4.82%)	8 (6.83%)	3 (2.7%)
SMA	1 (1.20%)	3 (2.56%)	3 (2.7%)
ARA	1 (1.20%)	0	0
AMA	0	0	1 (0.9%)
EMA	1 (1.20%)	0	0
Ribosomal	0	0	3 (2.7%)
Total	5*	11	10

HBV indicates hepatitis B virus; NOSA, non-organ-specific antibodies; ARA, antireticulin antibodies; AMA, antimitochondrial antibodies; EMA, antiendomy-sial antibodies.

\* One girl had ARA, ANA, and EMA.

production in 6-year-old immunized children. In the immunized group, there was a majority of girls compared with the control group (109 of 200 vs 34 of 109); because many autoimmune diseases are more prevalent in women than in men,<sup>17</sup> one would expect that the boys might have fewer autoantibodies than girls, so the comparison that we performed is even tougher for the immunized group.

Autoantibodies, referred to as natural autoantibodies, can be found in healthy individuals, but their significance is unclear.<sup>18,19</sup> These autoantibodies often cross-react with bacteria or tumor antigens, suggesting their importance in innate immunity.<sup>20,21</sup> It has been demonstrated in an animal model<sup>22</sup> that self-antigen can promote B-cell accumulation and that a significant proportion of natural autoantibodies is the product of this self-antigen-dependent process. Consequently, it has been speculated that self-antigens play a positive role in recruiting B cells as a part of innate immunity,<sup>22</sup> but this process carries a potential risk for unregulated growth. However, in our previous study, we demonstrated that patients who are affected by type 1 diabetes responded to rHBV and that no association existed between anti-HBsAg titer and the presence of organ- and/or non-organ-specific antibodies or other associated immune-mediated diseases.<sup>23</sup>

Spreading of the immune response is a common theme in organ-specific and systemic autoimmune diseases, and this could be initiated by exogenous agents, in genetically susceptible hosts, owing to molecular mimicry of natural antigen.<sup>11</sup> Moreover, 3 of the 16 children (18%) who had autoantibodies had a family history of autoimmune diseases. Thus, it is apparent that susceptibility to autoimmunity is determined by genetic factors rather than by vaccine challenge. Among all of the children considered, only 1 girl (0.5%) developed celiac disease, reflecting the prevalence described in the literature.<sup>24,25</sup> Moreover, the 2 different vaccination schedules applied did not affect autoantibody development. GADA and IA-2A were not found in our children; this observation is in agreement with the data of De Stefano et al,<sup>26</sup> who showed that type 1 diabetes risk may not be altered by vaccinations administered during childhood. On the contrary, a high frequency (30%) of autoantibodies, in particular SMA, was observed in the nonresponder children. The 3 SMA-positive children carried the HLA-C4AQ0,DRB1\*0301,DQB1\*02 haplotype, a widely known predisposing factor for autoimmune disorders. However, the presence of antibodies to smooth muscle is known to be common in hepatitis B infection, and it has been shown that cross-reactive immunity targeting homologous self-protein may partly account for autoantibody production.<sup>27</sup> Although hepatitis B vaccination given in neonatal age does not increase autoantibody production in 6-year-old immunized children, we deem useful a more prolonged follow-up for these nonresponder children carrying certain HLA haplotypes (eg, C4AQ0,DRB1\*0301,DQB1\*02), particularly because most autoimmune diseases do not develop until later in life.

**TABLE 2.** NOSA and HLA Typing in 10 Children Nonresponders to rHBv

Patient No.	Class (Gender)	NOSA	C4Aq0,DRB1*0301,DQB1*02
1	TNR (F)	Negative	Positive
2	TNR (F)	Negative	Positive
3	TNR (F)	Negative	Negative
4	SR (M)	SMA-positive	Positive
5	SR (M)	Negative	Negative
6	TNR (M)	Negative	Negative
7	TNR (M)	SMA-positive	Positive
8	TNR (M)	Negative	Negative
9	TNR (M)	SMA-positive	Positive
10	TNR (M)	Negative	Positive

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