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Original Article

Evaluation of immune response to hepatitis A vaccination and vaccine safety in juvenile idiopathic arthritis

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Abstract

Background: Autoimmune mechanisms and drugs used in treatment increase the risk of liver disease in patients with juvenile idiopathic arthritis (JIA) and hepatitis A virus (HAV) vaccination is important, especially in intermediate-endemicity areas like Turkey. In our study, we aimed to evaluate the immune response to hepatitis A vaccine and vaccine safety in children with JIA.
Methods: This study was carried out in our hospital's Pediatric Rheumatology outpatient clinic and Healthy Child clinic between the years 2003 and 2008. The study group consisted of 47 children with JIA (23 male and 24 female) diagnosed according to International League of Associations for Rheumatology diagnostic criteria. The control group consisted of 67 healthy children (31 female, 36 male) who did not have a history of hepatitis A infection or vaccination. Both groups were vaccinated with two doses of hepatitis A vaccine at 6-month intervals. Anti-HAV IgG >80 MIU was accepted as positive response.
Results: There was no significant difference between the groups in terms of age and sex. None of the patients with JIA had fever, clinical worsening, or disease activation after vaccination. Anti-HAV IgG positivity rate was significantly higher in the control group ($p < 0.05$). Anti-HAV IgG was negative in only four cases, and they were all male patients with systemic JIA who had active disease under anti-tumor necrosis factor treatment.
Conclusion: Hepatitis A vaccine was safe in patients with JIA, and response to vaccine did not differ between healthy children and patients with JIA except for children with active systemic JIA receiving anti-tumor necrosis factor alpha drugs.
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Keywords: Anti-hepatitis A IgG; Anti-tumor necrosis factor drugs; Hepatitis A vaccination; Juvenile idiopathic arthritis

1. Introduction

Hepatitis A is an acute, usually self-limiting disease of the liver caused by hepatitis A virus (HAV). HAV is transmitted from person to person, primarily by the fecal-oral route. The incidence of hepatitis A is closely related to socioeconomic development, and sero-epidemiological studies show that prevalence of anti-HAV antibodies in the general population varies from 15% to close to 100% in different parts of the world. In areas of low endemicity, hepatitis A usually occurs as single cases among persons in high-risk groups or as outbreaks involving a small number of persons. In areas of high endemicity, most people are infected with HAV without symptoms during childhood. In areas of low and intermediate endemicity, transmission occurs primarily from person to person in the general community, often with periodic outbreaks. In these countries, many individuals escape early childhood infection, but are exposed later in life, when clinical hepatitis occurs more frequently. In these areas, most cases occur in late childhood and early adulthood, and hepatitis A infection has more severe clinical progress and is the most common cause of liver transplantation.[1,2]

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Juvenile idiopathic arthritis (JIA) is the most common rheumatologic disease of childhood with unknown etiology.[3] Although chronic joint involvement is the most common feature, it is a multi-systemic disease in which fever, rash, nephritis, carditis, and uveitis can also be seen. It is diagnosed on the basis of clinical findings and with exclusion of other possible diseases according to American Rheumatology College and International League of Associations for Rheumatology[4,5] criteria. In patients with JIA, both autoimmune mechanisms and drugs used in treatment increase the risk of liver toxicity. Furthermore, immunosuppression increases the risk of infection, therefore vaccination gains importance. There are very limited data about the safety and immunogenicity of hepatitis A vaccine. Many doctors believe that vaccination increases the risk of relapse in rheumatologic diseases. As a result, vaccination in these patients shows significant variation and leads to insufficient immunization. In this study, we aimed to evaluate the immune response to hepatitis A vaccine and vaccine safety in children with JIA.

2. Methods

This study was carried out in our hospital's Pediatric Rheumatology outpatient clinic and Healthy Child clinic between the years 2003 and 2008.

The study group (Group 1) consisted of 47 children with JIA (23 male and 24 female) diagnosed according to International League of Associations for Rheumatology diagnostic criteria that were republished after the Edmonton Arrangement in 2001.[6] The parents were questioned about vaccination of their children against hepatitis A and hepatitis infection anamnesis. Hepatitis A antibodies (anti-HAV IgM and IgG) were studied by macro enzyme-linked immunosorbent assay with Macro Access auto-analyzer in all of the children with no anamnesis of vaccination and hepatitis A infection.[7] Anti-HAV IgG >80 MIU was accepted as positive response. Children in whom anti-HAV IgG was negative were included in the study. None of the children had anti-HAV IgM positivity. Children with chronic disease other than JIA and children who did not regularly come to follow-up were excluded.

The control group (Group 2) consisted of randomly selected 67 healthy children (31 female, 36 male) with similar age and sex as the study group who applied to our outpatient clinic for several health certificate or screening tests and who did not have a history of hepatitis A infection or vaccination. Anti-HAV IgM and IgG were evaluated in all of the children. Children with negative anti-HAV IgG were included in the study. None of the children had anti-HAV IgM positivity.

Disease activity was evaluated with the Childhood Health Assessment Questionnaire (CHAQ).[8] Children who did not have any complaints in the last 6 months with CHAQ scores less than 0.5 were accepted as being in remission. Children who had symptoms of JIA in the last 6 months and children who had to take additional drugs with CHAQ scores higher than 0.5 were accepted as being in active phase.

Informed consent was obtained from the parents of all of the children. The study was approved by the ethics committee of the hospital. Both groups were vaccinated with two doses of hepatitis A vaccine at 6-month intervals. Anti-HAV IgG titers were evaluated at an average of 2 months after the second dose of hepatitis A vaccine.

NCSS 2007&PASS 2008 Statistical Software (NCSS, Kaysville, UT, USA) was used for statistical analysis. The qualitative data were evaluated using χ^2 and Fisher's exact test. Significance was accepted at $p < 0.05$ level.

3. Results

This study was carried out between October 2003 and October 2008 in our hospital's Pediatric Rheumatology outpatient clinic and Healthy Child clinic. The study group consisted of 47 patients (24 female, 23 male) with JIA with a mean age of 10.73 ± 3.89 years, and the control group consisted of 67 healthy children (31 female, 36 male) with a mean age of 9.41 ± 3.80 years. There was no statistically significant difference between the groups in terms of age and sex ($p > 0.05$) (Table 1).

In the study group, 14.9% of the children had systemic JIA, 12.7% had rheumatoid factor-negative polyarticular JIA, 2.1% had rheumatoid factor-positive polyarticular JIA, 36.2% had

Table 1
Distribution of demographical features of the study and control groups

		Study group	Control group	p[a]
Age (yr) (mean ± SD)		10.73 ± 3.89	9.41 ± 3.80	0.051
		n (%)	*n* (%)	p[b]
Sex	Female	24 (51.1%)	31 (46.3%)	0.253
	Male	23 (48.9%)	36 (53.7%)	
HBsAb Titers (mean ± SD) (median)		134.62 ± 111.76 (113.43)	265.83 ± 130.63 (288.64)	0.001[c]
		n (%)	*n* (%)	p[b]
Humoral response to hepatitis B vaccine	Negative	4 (8.5%)	1 (1.5%)	0.001[c]
	Positive (>10 mU/mL)	43 (91.5%)	66 (98.5%)	

[a] Student *t* test.
[b] χ^2 test.
[c] $p < 0.01$.
SD = standard deviation.

Table 2
Distribution of patients with JIA in terms of disease subtypes, drugs they used and disease activity

		n	%
JIA subtypes	Systemic JIA	7	14.9
	RF-negative polyarticular JIA	6	12.7
	RF-positive polyarticular JIA	1	2.1
	Oligoarticular JIA	17	36.2
	Extended oligoarticular JIA	1	2.1
	Enthesitis-related JIA	15	32
Drugs used	Anti-TNF	4	8.5
	NSAIDs	5	10.6
	MTX	29	61.7
	Prednisolone	12	25.5
	Salazopyrine	19	40.4
	MTX—Prednisolone	11	23.4
Disease activity	Remission without drugs	11	23.4
	Remission with drugs	28	59.6
	Active	8	17

JIA = juvenile idiopathic arthritis; MTX = methotrexate; NSAIDs = non-steroidal anti-inflammatory drugs; RF = rheumatoid factor; TNF = tumor necrosis factor.

oligoarticular JIA, 2.1% had extended oligoarticular JIA, and 32% had enthesitis-related JIA (Table 2).

Five (10.6%) of the patients used non-steroidal anti-inflammatory drugs, 4 (8.5%) anti-tumor necrosis factor (anti-TNF) drugs (etanercept 0.4 mg/kg twice a week for 5–6 months), 29 (61.7%) methotrexate (MTX), 12 (25.5%) prednisolone, 19 (40.4%) salazopyrine, and 11(23.4%) used MTX together with prednisolone (Table 2).

Among patients with JIA, 23.4% of the patients were in remission with drugs, 59.6% were in remission without drugs, and 17% had active disease (Table 2).

Anti-HAV IgG positivity showed statistically significant difference between the groups ($p < 0.05$); only four of the patients had negative titers, and they were all from the study group. They were all male patients with active systemic JIA and were on anti-TNF treatment (Table 3).

No side effects were encountered in any of the patients. No reactivation was seen and there was no increment in CHAQ scores.

4. Discussion

HAV is the most common cause of hepatitis in childhood and an important public health problem, especially in intermediate-endemic areas like our country.[9] It is also the most common cause of fulminant hepatic failure in Turkish children[10] as well as in many other countries around the world.[11,12] According to the World Health Organization, approximately 1.5 million clinical cases of hepatitis A occur worldwide annually,[1] but seroprevalence data indicate that tens of millions of HAV infections occur each year. In areas of moderate endemicity, HAV is not transmitted as readily because of better sanitary and living conditions, and the average age of infection is higher in these areas than in areas of high endemicity.[13] Paradoxically, the potential for large outbreaks of hepatitis A can be increased in comparison with highly endemic areas, because there is a larger pool of susceptible older children and adults (compared with high-endemicity countries) who are at high risk of infection and who, when infected with HAV, are likely to develop symptomatic illness.[14] The best way of controlling HAV endemicity is vaccination. Hepatitis A vaccines currently licensed are prepared from inactivated HAV and are equivalent in terms of immunogenicity and efficacy; however, some medical conditions that cause immunosuppression might reduce immune response.

Vaccination is an important process in children and adolescents with inflammatory rheumatologic disease. Active infection can lead to severe problems especially in immunosuppressed cases. Russo et al. reported two JIA cases who developed macrophage activation syndrome after hepatitis A infection.[15] One of them entered remission after high-dose steroids and immunosuppressants, and the other died. In another case from England, a 20-year-old female with Still's disease who had hepatitis A was diagnosed with virus-associated hemophagocytic lymphohistiocytosis,[16] and one case from China with systemic-onset JIA developed macrophage activation syndrome after hepatitis A infection.[17]

There is insufficient data on vaccine safety and efficacy in patients with JIA. In inflammatory diseases, response to vaccination shows significant variation and can lead to insufficient immunization. Furthermore, vaccination time has to be carefully chosen, and disease activity must be considered.[18]

Among children aged 1–18 years, 97–100% had protective antibody levels 1 month after receiving the first dose of vaccine, and 100% had protective levels with high geometric mean antibody concentrations 1 month after the second dose.[19,20] Antibody sensitivity differences are not clarified yet in chronic rheumatologic diseases and immunosuppressed patients.[21–24] Among our patients, independent of disease activity—whether the patient was in remission with or without drugs or had active disease—anti-HAV IgG was positive in all of the cases. However, because titration was not possible, we could not make a detailed comparison between the disease subtypes and activity. The titers were negative in only four of the patients with active disease receiving anti-TNF drugs.

TNF-alpha, a proinflammatory cytokine, has an important role in naturally acquired immunity, cell regulation, differentiation and apoptosis. It is released from macrophages, lymphocytes, somatic cells and immune cells. It also has a role in B and T lymphocytes, monocyte, and macrophage maturation. It

Table 3
Distribution of anti-HAV IgG in healthy children and children with JIA after hepatitis A vaccination

		Study group	Control group	p[b]
		n (%)	*n* (%)	
Anti-HAV IgG	Negative	4 (8.5%)	0	0.027[a]
	Positive	43 (91.5%)	67 (100%)	

[a] $p < 0.01$.
[b] Fisher's exact test.
HAV = hepatitis A virus; JIA = juvenile idiopathic arthritis.

increases thymocyte proliferation in the presence of IL-1, IL-2, and IL-7. Studies on the effects of anti-TNF drugs on immune response to vaccination are very few. In one study by Kapetanovic et al. on patients with rheumatoid arthritis after influenza vaccination, it was shown that patients treated with TNF blockers alone or in combination with MTX and/or other disease modifying antirheumatic drugs had lower number of responders to the vaccine.[25] However, the mechanism of action is still under debate. During etanercept use, cellular response and accordingly humoral response are affected and the risks of tuberculosis, parasitic and viral infections increase. Although low anti-HAV titers after vaccination can be related to etanercept treatment, three of four patients had active disease and were receiving immunosuppressive drugs like MTX, which can also have a role in decreased vaccine response.

In clinical trials, the most frequently reported side effects of hepatitis A vaccine include soreness at the injection site, headache, and malaise.[26,27] These symptoms rarely last for more than 48 hours. None of the licensed hepatitis A vaccines have been associated with any serious adverse events in large prelicensure or post-marketing studies.[28−30] In our patients, we also did not encounter any side effects, even in patients receiving anti-TNF drugs.

In conclusion, we can say that hepatitis A vaccine is safe and immunogenic in patients with JIA, and response to vaccine did not differ between healthy children and patients with JIA except for children with active systemic JIA receiving anti-TNF alpha drugs.

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