Decreased antibodies against hepatitis A in previously vaccinated treatment naïve juvenile SLE patients: a prospective case control study

Sirs,

Juvenile SLE (jSLE) patients are susceptible to infections due to their defective immune system and the immunosuppressive treatment they receive (1). However we lack data regarding response to certain vaccine preventable diseases. Hepatitis A is an indolent disease with a varying clinical spectrum and consequences and also a vaccine avoidable disease with intermediate endimicity in Mediterranean countries (2).

In this study we aimed to define the immune status against Hepatitis A virus (HAV) in previously vaccinated jSLE patients, prior to commencement of treatment and at one and three years, and compare this to healthy controls.

This was a prospective controlled study including 21 newly diagnosed jSLE patients and 76 healthy controls. The control group consisted of healthy children matched for ethnic origin, age and gender to the jSLE group, attending the Paediatric Outpatients Department for routine checks; the same exclusion criteria applied. All participants had two doses of the inactivated Hepatitis A vaccine in early childhood. Exclusion criteria were underlying immunodeficiency, recent blood transfusion (<6 months) and previous treatment with immunomodulating agents. Demographic, clinical and laboratory data as well as data regarding immunisation status, vaccine history and mean time between the doses of the vaccine were collected. Seroprotection rates and anti-HAV-IgG titres were measured at enrolment and at timely intervals afterwards (0, 12, 36 months). Total IgG levels were measured simultaneously. HAV-IgG antibodies were assessed by ELISA. The cut-off value for seroprotection was deemed at 20IU/ml (3). The Hospital's Research and Ethics' Committee approved the study; written informed consent was obtained. Statistical significance was set at $p<0.05$ and analyses were conducted using SPSS (v. 19.0).

The two groups had similar demographic characteristics, vaccination history and immunisation status. No significant differences were detected in terms of vaccine type, time interval between the two groups as well as mean time from last vaccination to blood sampling. Seroprotection rates were adequate for both groups. Nonetheless, the jSLE group had consistently inferior (but not statistically meaningful) seroprotection rates at all time-points. Mean anti-HAV IgG antibodies were significantly lower in the jSLE compared to the control group ($p<0.01$). Similar results were found at one and three years' follow-up (Table I). None of the participants had hypogammaglobulinaemia at the time of blood sampling. During the follow up period, the jSLE group had greater decrease in antibody levels as indicated from the significant interaction effect of analysis. There was no association detected between degree of antibody loss and type of treatment or jSLE disease activity.

Table I. Demographic characteristics, seroprotection rates and mean anti-HAV IgG titers for the SLE and the control group.

Parameters	SLE group	Control group	*p*-value
Study sample, n	21	76	0.9*
Age, years, mean (SD)	11.3 (2.3)	10 (2.7)	0.8*
Gender n (%)			
female	20 (95%)	72 (95%)	0.83+
male	1 (5%)	4 (5%)	
Fully vaccinated	16 (71%)	62 (83%)	0.4+
Partially vaccinated (other than HAV)	5 (29%)	14 (17%)	
Type of vaccine given			
HAVRIX	34 (81%)	119 (78%)	0.84+
VAQTA	8 (19%)	33 (22%)	
Mean interval between doses (months)	19	23	0.3*
Mean time from last dose to sampling (years)	6	5.4	0.7*
Steroids (21/21)			
mean dose	10mg	NA	-
mean duration of treatment	17 months		
HCQ (21/21)			
mean dose	200mg		
mean duration of treatment	36 months		
Azathioprine (9/21)			
mean dose	75mg		
mean duration of treatment	18 months		
SLEDAI score			
Enrolment	7		
1 year	1		
3 years	0		
Seroprotection rate at diagnosis (%)	95	98	0.4+
Seroprotection rate at 1 years (%)	92	97	0.1+
Seroprotection rate at 3 years (%)	89	96	0.06+
Mean IgG titres at diagnosis, mIU/ml	167	249	<0.01*
Mean IgG titres at 1 year, mIU/ml	131	218	<0.01*
Mean IgG titres at 3 years, mIU/ml	134	202	<0.01*

p-value: *Student *t*-test, +Pearson's chi-square test.

This was a novel study concerning antibody status against Hepatitis A in children with jSLE. Fully vaccinated participants showed satisfactory seroprotection rates and antibody titres. Nonetheless, we detected increased antibody loss against Hepatitis A in children with jSLE, which further accelerated once treatment was initiated. Low antibody titres could be attributed to the disease (4), its activity (5) or medications (6). Studies concerning other vaccines, performed in children with IBD, JIA and jSLE showed matching results (7-9). The majority of patients with jSLE receive long-term immunosuppressive treatment. B-cell depletion observed in patients under immunosuppressive treatment is a well-documented factor leading to antibody depletion; hence the accelerated rate of antibody loss can be justified. Immunity against certain viruses is severely affected in patients receiving immunosuppressive treatment, rendering these patients susceptible to HAV infection (10). In fact, corticosteroids and immunosuppressants are associated with decreased vaccine serological response whereas hydroxichloroquine seems to improve vaccine immunogenicity (4). Additionally, steroid use seems to hamper immunogenicity in a dose dependent manner (6).

SLE is partially a lymphocyte-mediated autoimmune disease with abnormality in the adaptive immune system. Self-antigens set off reactive T cells including Th1 cells with production of pro-inflammatory cytokines. Defective Th1 reaction has been repeatedly reported in vaccine non-responders, rendering this hypothesis challenging for further insight (11). Our study was underpowered to bring up differences amongst the different treatment groups and correlate disease activity to antibody loss. Finally, although baseline immunology tests were carried out, further studies on B cell function were not performed.

In conclusion, although seroprotection rates were similar between the two groups, mean anti-HAV-IgG titres were significantly lower in the jSLE group at all time-points. Further studies are required to address the question of long-term immunity conveyed by immunisations given at an early stage in children with rheumatic diseases. However, evaluation of immunisation status against all vaccine preventable diseases in such patients may be beneficiary.

Key messages

- Children with autoimmune diseases show evidence of immune dysregulation
- Accelerated antibody loss against Hepatitis A is noted in children with jSLE

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