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Varicella vaccination in children with steroid-sensitive nephrotic syndrome

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Abstract We have studied serological and clinical response to live, attenuated varicella zoster virus (VZV) vaccine (Varilrix, SmithKline Beecham) in 20 patients with steroid-sensitive nephrotic syndrome (SSNS) in remission and 22 normal controls who had no history of varicella and no detectable antibody to VZV. Nephrotic patients included 15 boys and 5 girls, with a mean age of 4.7 years (range 2–11.4 years). The controls were healthy age-matched children (13 girls and 9 boys). Seventeen patients with SSNS (85%) and 19 healthy controls (86%) seroconverted 8 weeks after vaccination. One patient with SSNS had a relapse 20 days after vaccination, and 1 child in the control group had a rash. Two years after vaccination, antibodies to VZV were detected in 12 of 17 responders, 2 of 3 non-responders, and 13 of 22 controls. Within 2 years of vaccination, 3 of the vaccine responder children with SSNS had a mild varicella infection. Two responder and 1 non-responder nephrotic children and 9 controls were lost to long-term follow-up. Our results show that immunization with a single dose of VZV vaccine is safe and effective in children with SSNS in remission.

Keywords Varicella zoster virus · Vaccines · Nephrotic syndrome · Corticosteroids · Immunization

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Introduction

Varicella zoster virus (VZV) causes both varicella (chickenpox) and zoster (shingles). Varicella is the primary infection, which occurs in humans with no specific antibody or cell-mediated immunity to the virus. Varicella is mostly self-limiting in healthy children. Immunocompromised individuals with varicella infection are at risk of severe disease, with an increased morbidity and mortality. Zoster occasionally may become generalized in immunocompromised patients with visceral complications [1, 2]. Children with nephrotic syndrome receive high-dose steroids, and other immunosuppressive drugs in some cases, and therefore are at increased risk when infected with the VZV [1, 3, 4]. Varicella vaccine has been found to be safe in immunosuppressed children with leukemia, but experience with vaccine administration in immunosuppressed children with nephrotic syndrome is limited [5, 6, 7]. In this study, we investigated the efficacy and safety of varicella vaccine in children with steroid-sensitive nephrotic syndrome (SSNS).

Patients and methods

Twenty children, aged 2–11.4 years (mean 4.7±2.2 years), with idiopathic nephrotic syndrome, and 22 healthy children, aged 1.3–8.3 years (mean 4.1±1.8 years), were vaccinated with a live attenuated VZV vaccine (Varilrix, SmithKline Beecham) at the Department of Pediatric Nephrology SSK Göztepe Hospital, Istanbul, Turkey. Informed consent was obtained from every subject after a full explanation of the study. The nephrotic children included 15 (75%) boys and 5 (25%) girls, and there were 14 girls and 8 boys in the control group.

All the nephrotic patients had at least one episode of proteinuria in excess of 1 g/m^2 per day with hypoalbuminemia and peripheral edema. They were all steroid responsive and were in remission or had already stopped steroid therapy at least 6 weeks before vaccination. No recent administration of blood, plasma, or immunoglobulin was noted.

The children with SSNS and the control group had no history of varicella or any detectable antibody to VZV before vaccination. Varicella virus vaccine (Varilrix, SmithKline Beecham), 0.5 ml per dose containing a minimum of 1,350 plaque-forming units of attenuated OKA line, was administered subcutaneously.

Table 1 Response to varicella vaccine in children with steroid-sensitive nephrotic syndrome (+ seropositive, – seronegative, *NA* not available, *NC* not collected because of the varicella infection)

Patients	Pre-vaccination	8 weeks post vaccination	2 years post vaccination	Side effects	Varicella infection
1	–	+	+		+
2	–	+	+		–
3	–	+	NA		–
4	–	+	+		–
5	–	+	NA		–
6	–	–	+		–
7	–	+	+		–
8	–	+	NA		–
9	–	+	+		–
10	–	+	+		–
11	–	+	NC	Relapse in 20 days	+
12	–	+	+		–
13	–	+	+		–
14	–	+	NC		+
15	–	+	+		–
16	–	–	+		–
17	–	+	+		–
18	–	+	+		–
19	–	+	+		–
20	–	–	NA		–

Children were monitored for 8 weeks after vaccination. The follow-up included parental monitoring for any signs of reaction to the vaccine, such as fever, rash, local pain, tenderness, fatigue, and evidence of proteinuria by urine dipstick. Families were also asked if chicken pox was suspected and were seen by the physician until the second evaluation of the patients. Serum samples were obtained prior to vaccination, at 8 weeks for the first evaluation of vaccine response, and at 2 years for the second evaluation of the vaccine response. They were immediately frozen and stored at –20°C until testing. Antibodies to VZV were measured by ELISA using Varicella-Zoster IgG/IgM kit (VIRCELL SL). Mean negative control (MNC) and mean positive control (MPC) values were determined and the cut-off values (COV) were calculated with the formula COV=0.1×MPC+MNC. Antibody titers greater than COV+15 were considered positive and less than COV–15 were considered negative. Samples with a predictive index between these values were considered suspicious and retested 7–14 days later.

Results

The response to varicella vaccine in nephrotic children is presented in Table 1. Seventeen patients (85%) with SSNS and 19 healthy children (86%) seroconverted 8 weeks post vaccination. Vaccine response in the group of SSNS patients was not different from that in the control group at 8 weeks ($P>0.05$). VZV IgG antibodies were remeasured in 14 of 20 nephrotic patients and in 13 controls 2 years after vaccination. All of the children tested at the second evaluation had seroconverted. The antibody titers were not measured at the second evaluation in 6 nephrotic children. Two of them developed mild chickenpox, although they had seroconverted by the 8th week, and 4 children, 3 seropositive and 1 seronegative, were lost to follow-up. Nine children in the control group were also lost to follow-up. Two of them were seronegative and 7 were seropositive 8 weeks post vaccination. Two children with SSNS and 1 control who seemed to be a non-responder at the first evaluation had seroconverted within 2 years.

In the SSNS group, 1 child had a relapse of the nephrotic syndrome 3 weeks after vaccination. Four patients relapsed in 5–12 weeks after vaccination, but these relapses followed the same pattern as their previous relapses. All children responded to the subsequent corticosteroid therapy.

Modified chickenpox occurred in 3 patients with SSNS. Two children were seropositive at 8 weeks and developed chickenpox before the second evaluation. To our surprise, 1 child who was seropositive at both evaluations developed chickenpox after the second evaluation. These patients had a very mild form of chickenpox, with only a few vesicular lesions, and all reported exposure history.

In the control group, the only reported adverse effect was a generalized evanescent rash in 1 child. None of the children in the control group developed chickenpox within 2 years of follow-up.

Discussion

Varicella is a common contagious disease of childhood that is caused by primary infection with VZV. In normal children, the systemic symptoms are usually mild and serious complications are unusual [1].

Immunocompromised children are predisposed to develop severe varicella infection with a potentially fatal outcome. Varicella can be a very serious disease, with visceral complications, in patients receiving high doses of corticosteroids and patients treated with chemotherapy or radiotherapy for an underlying malignancy [3, 4, 8]. Serious varicella infection may occur in children with nephrotic syndrome, because of their immunosuppressive therapy with steroids and other drugs. Therefore, it is important to vaccinate the children with SSNS susceptible to VZV infections to eradicate varicella and its

complications. Recent guidelines from both the American Academy of Pediatrics (AAP) and the Advisory Committee on Immunization Practices (ACIP) regarding the use of varicella vaccine in children on steroid therapy suggest that live attenuated varicella vaccine may be safely given in children receiving prednisone less than 2 mg/kg per day or less than 20 mg/day in a child who weighs more than 10 kg. The ACIP states that short term, low-to-moderate-dose steroids and long-term alternate-day treatment with short-acting preparations usually do not contraindicate administration of live virus vaccine [1, 9]. Our patients were in remission or had already stopped steroid therapy at least 6 weeks before therapy.

We found the varicella vaccine in children with SSNS as effective as in healthy children, with a seroconversion rate of 85% and 86%, respectively. Our result is similar to other investigators who found the seroconversion rate to be greater than 95% after one dose of vaccine [1, 10, 11]. Quien et al. [7] found that the antibody response to varicella vaccination was variable, with only 3 of 7 patients seroconverting after one dose. However, all patients seroconverted after the second dose. Besides the persistence of varicella antibody titers until the second evaluation, 2 of 3 unresponsive nephrotic children and 1 of 3 unresponsive healthy children seroconverted within 2 years without a second dose of vaccine. One nephrotic and 2 healthy unresponsive children were lost to follow-up, and so we were not able to test whether they seroconverted during the 2-year follow-up.

Adverse events following vaccination were minimal. Modified chickenpox developed in 3 children with SSNS who had protective antibodies within 2 years of vaccination. A mild varicelliform rash occurred in only 1 child in the control group 20 days after vaccination. Within a month of immunization, a mild vaccine-associated maculopapular or varicelliform rash may develop in approximately 3%–7% of healthy children. It is recognized that the presence of specific serum antibody does not necessarily guarantee protection from clinical varicella infection with an exposure several months after immunization. As other investigators have reported, our cases of modified chickenpox were considerably milder than the natural disease [1, 11, 12, 13, 14].

One child had a relapse of the nephrotic syndrome 3 weeks after vaccination. This child had two relapses in 49 months before he was vaccinated. The relapse of this child might have been precipitated by vaccination, but the role of the vaccine in the relapse is not known exactly. Quien et al. [7] observed three relapses in 3 of 7 children with nephrotic syndrome, but those relapses represented their previous pattern of relapses. Although it is widely accepted, there are no definite data to support the exacerbation or precipitation of relapses in minimal change nephrotic syndrome by immunization. A questionnaire, answered by members of the American Society of Pediatric Nephrology, showed that consensus for immunization does not exist, and individual physicians have their own approaches [15]. This investigation shows that varicella vaccine is safe and effective in children with SSNS, even with a single dose, and VZV vaccination is recommended for children with SSNS because of the increased frequency and severity of varicella infection. However, the long-term persistence of serum antibody, clinical efficacy, and the role of the vaccine in the precipitation of relapses of nephrotic syndrome must await further evaluation.

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