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The early and late response of pneumococcal vaccination in nephrotic children

Harika Alpay, Neşe Karaaslan Bıyıklı*, Tunç Akkoç, İbrahim Gökçe, Nihal Özdemir, Nurdan Yıldız

Marmara University School of Medicine, Department of Pediatric Nephrology, Istanbul, Turkey

Objectives: Pneumococcal infection is frequent and severe in patients with nephrotic syndrome (NS). Pneumococcal polysaccharide vaccine is recommended for nephrotic children older than 2 years of age. The aim of our study is to assess the clinical and laboratory efficiacy and side effects of pneumococcal polysaccharide vaccine in NS patients.

Methods: 27 children with steroid responsive NS and 20 controls were enrolled in the study. A 23 valent pneumococcal polysaccharide vaccine was used for vaccination. Blood samples were obtained before and 4 weeks and 3 years after vaccination. ELISA test was used to quantitate serum total antipneumococcal capsule polysaccharide immunoglobulin G antibodies. Antibody levels before vaccination, 4 weeks and 3 years after vaccination were compared.

Results: The mean age of the nephrotic children and controls were 7.8±3.1 years and 8.6±2.6 years, respectively. Baseline antibody titers and antibody titers following 4 weeks and 3 years of vaccination for nephrotic children and controls were 33.3±18 mg/L, 100.9±22.2 mg/L, 135.5±114.2 mg/L and 32.8±13 mg/L, 101.6±41.1 mg/L, 144.3± 64 mg/L, respectively. The increase in pneumococcal antibody levels in the 4th week ($p<0.05$) and the persistence of antibodies in the 3 year ($p<0.05$) were statistically significant and similar to the increases observed in the control group. 60% of the patients preserved their protective antibody levels at the 3rd year evaluation. None of the children showed neither side effects nor a pneumococcal infection episode during the study period.

Conclusion: We conclude that pneumococcal polysaccharide vaccine is a well tolerated and immunogenic vaccine in nephrotic children. Revaccination may be considered in nephrotic children after the assessment of antibody levels 3 years after vaccination.

Key words: Nephrotic syndrome, pneumococcal polysaccharide vaccine, child, vaccine efficiacy

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*Correspondence to: Neşe Karaaslan Bıyıklı, MD
Kozyatağı, Sinanercan Cad,
Oztor Sitesi, C Blok, 38/38,
Istanbul 34736 Turkey
Phone: + 90 216 372 71 07
e-mail: nesebiyikli@superonline.com
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Introduction

Pneumococcal infection is frequent and severe in patients with nephrotic syndrome because of decreased serum and peritoneal fluid levels of immunoglobulins and complement proteins.[1-3] Streptococcus pneumoniae is an encapsulated bacterium with 90 known capsular serotypes and 40 serogroups, distinguishable by the structure of the polysaccharide capsule.[4] Pneumococcal polysaccharide vaccine has become the standard care for several population groups, including infants, elderly persons and patients with human immunodeficiency infection, hematologic malignancy, nephrotic syndrome, chronic renal failure and solid organ transplantation.[5] The vaccine induces serotype-specific antibodies that enhance the opsonization and killing of pneumococci.[5] Vaccine studies report that responsiveness to vaccination in patients with renal disease can be diminished and the issue of pneumococcal vaccine efficacy is of increasing importance for nephrotic patients.[6] The 23 valent pneumococcal polysaccharide vaccine include 23 serotypes that has efficiacy to more than 85% of invasive infections.[5] The American Academy of Pediatrics (AAP) recommends that all children with nephrotic syndrome should receive a single dose of pneumococcal polysaccharide vaccine if they are at least 24 months of age, with a single booster 3-5 years later if they were younger than 5 years old when they received the first dose.[5] The initial response to the vaccine and the duration of immunity by efficient anti-pneumococcal polysaccharide vaccine antibody titers over time are still controvertial.

Aim of our study is to assess the clinical and serological efficiacy and side effects of 23 valent pneumococcal polysaccharide vaccine in the early and also late phase of vaccination in nephrotic children.

Materials and Methods

27 patients with steroid sensitive nephrotic syndrome and 20 healthy children with no history of a chronic illness were included in this prospective study. All patients had been in remission for at least 6 months (median: 13 months, range 6-115 months) at the time of vaccination. Nephrotic subjects had not received corticosteroids for at least 3 months. None of them had previously been vaccinated by pneumococcal polysaccharide vaccine.

The parents and patients were informed about the study and fully informed consent was taken from the families. Patients and controls were vaccinated im with a commercial 23-valent pneumococcal polysaccharide vaccine (Pneumo 23, Pasteur Merieux), each containing 25 microgram of capsular antigene of the serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22, 23F, 33F (0.5 ml). Blood samples were obtained before the vaccination and at 4 weeks and 3 years after vaccination. Baseline and 4th week blood samples were taken from all subjects. The 3rd year serum sample were available for 25 nephrotic children and 16 controls. Serum were seperated and kept at –20 C until testing. All samples were studied at the same time. Standard enzyme-linked immunoabsorbant assay (ELISA) was used to quantitate serum specific IgG antibodies against Pneumococcal Capsular Polysaccharide (MK012 anti-PCP Ig G enzyme immunoassay commercial kit; the Binding Site Ltd, Birmingham, UK). The patients at least a twofold increase in the antibody titers after vaccination compared with the prevaccination levels were defined as the "antibody responders".[7] Fold increases in ELISA titers were determined by dividing the postvaccination titer by the prevaccination titer. Patients were asked for any symptoms occurring after vaccination. Infectious history and nephrotic syndrome relapse history during the study period was recorded.

Statistical analysis was performed using SPSS software package, version 10.0. Laboratory data were expressed as mean ± SD. Chi square test was used for the comparison of antibody titers between groups. Results were considered significant when the p value was less than 0.05.

Results

The study population included 27 nephrotic patients (11 girls and 16 boys), and 20 control subjects (8 girls and 12 boys). The mean age of the nephrotic children and controls were 7.8±3.1 years and 8.6±2.6 years, respectively. The mean baseline antibody titers and antibody titers following 4 weeks and 3 years of vaccination for nephrotic children and controls were 33.3±18 mg/L, 100.9±22.2 mg/L, 135.5±114.2 mg/L and 32.8±13 mg/L, 101.6±41.1 mg/L, 144.3±64 mg/L, respectively (Table 1). The titer increased at least twofold in 25 nephrotic patients (92.5%) at the 4th week evaluation. Mean increase was 3.9±2.3 fold (range: 1.3-11.3). Though there was an increase in postvaccination antibody levels in 2 patients, these increments did not reach to a twofold level; the first patient's antibody level increased to 132 mg/L from 80 mg/L (1.6 fold increase) and the second patient's antibody level increased to 72 mg/L from 57 mg/L (1.3 fold increase). All of the control subjects had increased titers of antibody levels greater than twofold increase.

Table 1
Anti pneumococcal antibody titers of the study population

	Nephrotic patients	Control subjects
	Pneumococcal antibody titer/number of patients studied	Pneumococcal antibody titer/number of patients studied
Baseline	33.3±18 mg/L / 27	32.8±13 mg/L / 20
4th week	100.9±22.2 mg/L / 27	101.6±41.1 mg/L / 20
3rd year	135.5±114.2 mg/L / 25	144.3±64 mg/L / 16

The third year evaluation revealed that 15 patients out of 25 (60%) continued to have antibody levels that is equal or greater than twofold increase from baseline and 10 patients (40%) showed antibody levels lower than the twofold increase from the baseline value.13 out of 16 controls (81%) showed antibody levels greater than the twofold increase from the baseline value at the 3rd year of vaccination.

The increase in pneumococcal antibody levels in the 4th week ($p<0.05$) and the persistence of antibodies in the 3rd year ($p<0.05$) were statistically significant and similar to the increases observed in the control group (Table 1). None of the children showed side effects such as local tenderness, erythema, fever, nausea, fatigue after vaccination and none of the patients experienced any pneumococcal infection during study period. Antibody persistence at the 3rd year was decreased in nephrotic patients compared with controls but without a statistically significant difference between (60% in nephrotics versus 81% in controls, $p> 0.05$). None of the patients experiened a relapse during study period.

Discussion

Our study showed the changes observed in the antibody levels of nephrotic children after pneumococcal polysaccharide vaccine both in the early and late phases. We observed that although the majority of the (92.5%) children with nephrotic syndrome showed a good initial response to pneumococcal polysaccharide vaccine, only 60% of them kept their antipneumococcal antibody levels in a stable high concentration for 36 months duration. The persistence of antibody levels equal or greater than twofold increase was 81% in the healthy children. The data revealed that antibody persistence declined in nephrotic patients in respect to controls though it did not reach to a statistically significant level. This may be due to the small sample size of the patients and controls.

Studies of response to pneumococcal polysaccharide vaccine in nephrotic patients are very few and all have small sample size. Wilkes et al reported the initial response of 14 valent pneumococcal polysaccharide vaccine in 20 nephrotic patients and showed that a mean of 8.4 fold increase was observed after vaccination.[8] Lee et al found that mean 3 fold increase in titers was observed in 48 children with nephrotic syndrome after vaccination by 14 valent pneumococcal polysaccharide vac-

cine.[9] Fucshuber et al reported the results of 23 valent pneumococcal polysaccharide vaccine in 9 nephrotic children in which 89% of them achieved a protective level of antibody response.[10] Our early phase results are paralel to these studies with a 92.5% of vaccine efficacy supported by the at least twofold (mean: 3.9±2.3) increases of antibody titers in respect to baseline antibody titers. The initial response of nephrotic children were in corcondance with the control group.

Only very few studies reported the long term results of antibody persistence. Guven et al reported the results of 9 patients with steroid sensitive nephrotic syndrome.[11] They showed that although all 9 patients reached to a antibody level of at least twofold after vaccination, but only two patients showed protective antibody levels for 36 months duration. Tejani et al reported the long term results of 13 valent pneumococcal polysaccharide vaccine in 16 children.[12] The study results showed that 56% of the patients who were minimal change nephrotic syndrome had enough antibody titers at 5 years.[12] Our results showed the largest number of nephrotic patients reported with the long term antibody data.

The majority of our patients (92.5%) have a good initial response and 60% of them kept their protective level of antibodies at the 3rd year. Nephrotic subjects may have ineffective antibody responses because of abnormal T cell function and may display an asymetric depression of serum IgG2 subclass concentration.[13] IgG2 subclass depression has been associated with decreased antibody concentration against pneumococcal polysaccharides after vaccination.[13,14] The persistence of protective antibody levels may be lower because of these immunological alterations in nephrotics.

Radioimmunoassay (RIA) and ELISA are methods of investigation of antipneumococcal antibodies. Previous studies used RIA and reported an antibody level of 200 ng of protein nitrogen as "protective".[15,16] This assay measured both IgG and IgM antibodies to type-specific capsular polysaccharides, as well as antibodies to the common pneumococcal cell wall C-polysaccharide.[14,15] The later antibody does not provide protection and may not be relevant to assessing immunologic protection from disease.[17] The ELISA assay measures type specific anti capsular pneumococcal IgG after C-polysaccharide absorption. ELISA is superior to RIA as it measures only protective antibodies to the pneumococcal capsular polysaccharides.[18] As for protection against pneumococcal infections, it is shown that IgG class antibodies are more important because they are known to promote the opsonophagocytosis more efficiently than IgM class antibodies.[19] We also analysed the antipneumococcal antibody titers by ELISA test that makes our results more reliable than the earlier studies.

Different serological approach such as antibody fold increase, antibody concentration, threshold antibody level or antibody function are considered to test serological vaccine effectiveness. In our study we used antibody fold increases. Studies of vaccine efficiacy showed that a twofold increase in antibody concentration after vaccination could be considered as protective.[7] As a T cell independent antigen, the 23-valent pneumococcal capsular polysaccharide vaccine is not expected to induce memory or affinity maturation of the antibodies; therefore, the antibody concentration measured is likely to reflect protection from disease.[6]

In conclusion, pneumococcal polysaccharide vaccine is well tolerated, immunogenic and effective at the early phase in nephrotic children. Late phase results showed that antibody persistence is lower in nephrotic patients. If needed serological response can be tested at the 3rd year and revaccination may be considered in those with lower antibody titers.

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