

Assessment of Antibody Titer to Pneumococcal Vaccine in Nephrotic Syndrome Children post Vaccination

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ABSTRACT

Background: The most common glomerular condition in children is idiopathic nephrotic syndrome (INS). Pneumococcal infections are one of the most serious consequences for children with nephrotic syndrome. **Objective:** Assessment of antibody titer in children with renal impairment 1- and 3-months after immunization with pneumococcal conjugate vaccine 13 (PCV13). **Patients and Methods:** Cross-sectional research including 24 nephrotic children was carried out at Pediatric Nephrology Unit and Outpatient Nephrology Clinics of Children Hospital at Zagazig University over a period of one year from April 2020 to March 2021. **Results:** At 1- and 3-months following vaccination, level of antibody titer was significantly higher among patients within group II. There was statistically significant difference between the studied groups regarding trend of antibody at three months. Steroid dosage at time of immunization was strongly associated with antibody titer one month (M) after vaccination in both groups. While there was statistically significant negative correlation between steroid dose at time and 3 months after vaccination with antibody titer at 3 months post vaccination in both groups. **Conclusion:** Nephrotic children in both groups can mount adequate antibody production to pneumococcal vaccine post vaccination, which is equal or higher than 0.35 µg/ml. On low doses of oral steroids and immunosuppressive medications, PCV-infected nephrotic youngsters developed strong protective antibody titers.

Keywords: Nephrotic syndrome, Pneumococcal Vaccine, Post Vaccination.

INTRODUCTION

The prevalence of bacterial infections in children with nephrotic syndrome (NS) has reduced in industrialized nations, but they remain a substantial issue in poor countries. Sepsis is still a leading cause of death in children with NS, whereas peritonitis is a major source of morbidity and mortality in NS patients, and *Streptococcus pneumoniae* is the most common bacteria responsible for primary peritoneal peritonitis (4, 2). Resistance to conventional antibiotics by *S. pneumoniae* highlights the urgent need to employ vaccinations in the fight against pneumococcal illness (3).

To combat pneumococcal illness, vaccinations are urgently needed since *S. pneumoniae* is becoming more and more resistant to treatments (4). Many medical experts are baffled by the technique for administering the NS pneumococcal vaccine to youngsters, resulting in many of these children not receiving an adequate vaccination (5).

While on high dose prednisolone for more than two years, *Ulinski et al.* (6) found that patients who received PPV23 during active disease were able to mount an antibody response of 10-fold increase on day 30 post vaccination, similar to that of NS patients who received vaccine in remission while on low dose prednisolone. One year after immunization, antibody levels in both groups were strong and no individuals developed invasive pneumococcal illness (7).

We aimed in this study to assess antibody titer to pneumococcal conjugate vaccine 13 in children with nephrotic disease 1- and 3-months post vaccination.

PATIENTS AND METHODS

Cross-sectional research including 24 nephrotic children was carried out at Pediatric Nephrology Unit and Outpatient Nephrology Clinics of Children Hospital at Zagazig University over a period of one year from April 2020 to March 2021.

Ethical considerations:

As long as all parents of participants signed informed consent forms and the study was agreed from Zagazig University's Research Ethics Committee, with number (ZU-IRB#6227). We followed the World Medical Association's ethical code for human experimentation, the Helsinki Declaration.

Inclusion criteria:

1. Diagnosed children with NS of both sexes and their age between 2 to 15 years were included.
2. Acute NS cases (newly cases after 1 month of daily steroid either early responder or late responder or steroid resistant NS (SRNS)).
3. Treated NS cases along 1 to 1.6 year (frequent, infrequent or resistant cases) and they were treated by relatively low doses of both corticosteroid and other immunotherapy.
4. All children of NS included in study were not vaccinated previously (either at the time of obligatory vaccines or later on).



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Exclusion criteria:

1. Nephrotic children older than 15 years at time of primary immunization.
2. Congenital and infantile NS.
3. Children who were previously vaccinated (either with obligatory vaccines or after this period).
4. All patients received medication before admission.
5. Refusal of parents or children to participate.
6. Any steroid therapy within 48 hours.
- 7.

Patients were classified into two groups:

Group I (Acute NS children): This group comprised 14 children of newly diagnosed nephrotic syndrome. The cases were assessed for the clinical, laboratory parameters at baseline. All our nephrotic patients had the criteria of NS in form of generalized edema, proteinuria > 40 mg/m²/h, hypoalbuminemia (serum albumin <2.5 g/dL) and hypercholesterolemia (serum cholesterol >200 mg/dL). The age of patients ranged from 2.8-8 years, both sexes were presented; 9 (64.3%) male and 5 (35.7% female). They were treated at Nephrology Unit of Pediatric Department of Children Hospital. All patients were on steroid 2 mg/kg/day and maximum 60 mg daily. Seven cases were early responder (steroid sensitive nephrotic syndrome (SSNS) who entered remission in response to steroids therapy alone within 4 weeks then completed same dose every day. Other 7 cases of NS children were steroid resistant NS (SRNS) who didn't respond to initial doses within one month and they took 3 pulses of intravenous methyl prednisolone on alternative day before renal biopsies were taken and continued on the same doses of steroids until biopsies results appeared. The results of biopsies were 2 cases minimal change nephrotic syndrome (MCNS) (14.3%), 4 cases focal segmental glomerulosclerosis (FSGS) (28.6%) and 1 case diffuse mesangial proliferation (DMP) (7.1%). Five cases of NS were treated by pulse intravenous methyl prednisolone every other day until remission was occurred and continued on steroid 2 mg/kg every other day and cyclosporine 5 mg/Kg/d divided on two doses for all cases. One case of SRNS was treated by pulses of intravenous methyl prednisolone for 6 doses and one dose of IV cyclophosphamide on 500 mg/m²/dose and continued on cyclosporine (MCNS). Last case of SRNS was treated by mycophenolate mofetil. All cases of this group were assessed clinically and laboratory at base line, at the time of PCV13 injection, after 1 and 3 months of PCV13.

Group II: This group comprised 10 cases nephrotic syndrome still under treatment but on low dose of steroid and immunomodulators either frequently relapsing nephrotic syndrome (FRNS) 4 cases (40%) and steroid dependent nephrotic syndrome (SDND) 3 cases (30%) and SRNS 3 cases (30%). The age of patients ranged from 3.5-6 years, both sexes were

presented (6 (60%) male and 4 (40% female). Within group II; 50% of included cases, biopsies were not done, MCNS (20%), FSGN (20%), DMP (10%). History for specific therapy was taken for group that revealed all cases treated by prednisolone, 70% by levamisole, 60% cyclosporine, 30% cyclophosphamide, 30% MMF and 10% plasmapheresis. Actual drugs at the time of PCV13 injection, 1 and 3 months after vaccines, were of steroid on dose range 5-20. Other immunomodulator on the other hand were cyclophosphamide (4 patients, 40%), MMF (3 patients, 30%) or cyclosporine (1 patients, 10%) and lastly only 2 cases were not on immunomodulator (20%). They were at follow up at Outpatient Nephrology Clinics of Children Hospital.

This is what all of the participants in this research had to go through:

1. History taking and clinical examination.
2. Assay of IgG for PCV13 titer either after 1 or 3 months for all cases in both groups.

One 0.5 ml dose of the pneumococcal conjugate vaccination (Prevenar; Wyeth; Madison, NJ, USA) comprised 16 g of saccharide serotypes and 20 cg of carrier protein CRM 197 and 0.125 mg of aluminum adjuvant (aluminum phosphate) in the vaccine, which was injected intramuscularly. Assay range in pamphlet was 0.5 ug/ml to 10 ug/ml. As suggested by the World Health Organization (WHO) for testing the efficacy of pneumococcal conjugated vaccines in babies, children, and young adults, 0.35 g/ml was the minimum or enough antibody production that was protective ⁽⁸⁾ either for at least five of the seven vaccine serotypes, a rise in IgG concentration post-vaccination that is at least two times the baseline value ⁽⁹⁾.

Statistical analysis

In order to analyze the acquired data, they were loaded into a computer and run via the Statistical Package for the Social Sciences, version 25. (SPSS). Tables were used to present the findings. The Shapiro–Wilk test was used to examine the distribution properties of variables as well as the homogeneity of variance. The quantitative data were reported in the form of the mean, standard deviation (SD), and range. The frequency and proportions of qualitative data were used to present the information. For quantitative independent data, the student's t test (T) and the Mann-Whitney test (MW) were employed to examine the data as needed. To examine qualitatively independent data, Fisher's exact test was used. P value equals or less than 0.05 was considered significant.

RESULTS

No statistical difference was found between the analyzed groups in terms of their age or their gender, according to table 1.

Table (1): Comparison of the study participants based on their demographics

Parameter	Groups		p
	Group I	Group II	
	N=14 (%)	N=10 (%)	
Gender:			
Female	5 (35.7)	4 (40)	1
Male	9 (64.3)	6 (60)	
Age (year):			0.565
Mean ± SD	4.521 ± 1.773	4.87 ± 0.729	
Range	2.8 – 8	3.5 – 6	

Table 2 shows that one and three months after immunization, level of antibody titer was significantly higher among patients within group II than group I. While there was statistically significant decrease in antibody titer of patients with group II after vaccination.

Table (2): Comparison between the studied patients according to antibody titer at 1 and 3 months post vaccination

Antibody titer	Groups		P
	Group I	Group II	
	Mean ± SD	Mean ± SD	
1 month of vaccination	0.762 ± 0.243	1.76 ± 0.538	<0.001**
3 months of vaccination	0.749 ± 0.161	1.39 ± 0.519	<0.001**
P	0.629	0.004*	

*: Statistically significant, **: Statistically highly significant

Statistically significant differences in antibody trends were found across the groups evaluated at three months (Table 3).

Table (3): Comparing the antibody change trends of the study groups after 3 months

Antibody titer trend	Groups		p
	Group I	Group II	
	N=14 (%)	N= 10 (%)	
Steady	1 (7.1)	0 (0)	0.007*
Increase	7 (50)	0 (0)	
Decrease	6 (42.9)	10 (100)	

*: Statistically significant

Table 4 shows that there was a highly significant negative correlation between steroid dose at time of vaccination and antibody titer 1 month after vaccination in both groups. While there was statistically significant negative correlation between steroid dose at time and 3 months after vaccination with antibody titer at 3 months post vaccination in both groups.

Table (4): Correlation between antibody titer and corticosteroid dose at time of vaccination and 3 months

Steroid dose	Group I		Group II	
	r	p	r	p
	Antibody titer at 1 month			
At time of vaccination	-0.683	0.007*	-0.953	<0.001**
Antibody titer at 3 months				
At time of vaccination	-0.628	0.016*	-0.811	0.004*
After 3 months	-0.863	<0.001**	-0.811	0.004*

*: Statistically significant, **: Statistically highly significant

DISCUSSION

When anti-PV injections are given, they are intended to protect the patient against severe pneumococcal infections as promptly as possible and to limit the danger of vaccination-induced relapses, or to diminish the fear of vaccination-induced relapses⁽¹⁰⁾.

A large majority of medical facilities prefer vaccinations during remission, as high-dose steroids and/or active NS therapy are thought to diminish the immune response and hence anti-pneumococcal antibody concentrations. Prednisone doses are typically decreased to 15 mg/m² body surface area every other day (EOD) or drugs are discontinued before immunization is administered⁽¹⁰⁾. But if this technique was utilised, anti-PV therapy for patients with steroid dependent or resistant NS would be delayed or not implemented at all. As previously mentioned, pneumococcal infections commonly develop during relapses or early stages of the illness. When steroids are tapered, patients will not have anti-pneumococcal antibodies, which is a period when the risk of recurrence is significant⁽⁶⁾.

The current study showed age of cases was 2.8-8 years in group I and 3.5-6 years in group II. This is in agreement with **Rhuma et al.**⁽¹¹⁾ who reported that INS is a disease of pre-school aged children with peak age incidence of 2-3 years. Also, **Saraswathi et al.**⁽¹²⁾ who reported that childhood NS can occur at any age but is most common between the ages of 1.5 and 5 years. They reported that age at initial presentation has an important impact on the disease distribution frequency and 70% of MCNS patients are younger than 5 years; 20-30% of adolescent nephrotic patients have MCNS⁽¹²⁾.

Our study showed obvious male predominance (64.3% in group I and 60% in group II) which is supported by **Rhuma et al.**⁽¹¹⁾ and **Ephraim et al.**⁽¹³⁾ who reported that INS affected males more than females. Current study showed no significant difference among studied as regard age and sex.

Our study showed that patients in both groups can mount adequate immunological response (antibody production) post-vaccination, which was higher than 0.35 µg/ml. In agree with World Health Organization (WHO) for assessing the efficacy of pneumococcal conjugated vaccines in infants and children and young adults, that minimum or adequate antibody production post-vaccination is 0.35 µg/ml⁽⁸⁾.

Our study showed a significant difference between the studied groups regarding antibody titer at 1 and 3 months after vaccination (level were significantly higher among patients within remission and in low dose of steroid and or immunosuppressive drugs (group II) than NS patients on high doses of both steroid and immunosuppressive drugs (group I) . There was a significant positive correlation between antibody titer at 1 month and all of total protein, serum albumin and a significant negative correlation between antibody titer

at 1 month and all of age, body weight at time of vaccination, after 1 and 3 months, platelet count, BUN, total cholesterol and albumin/creatinine ratio. In contrary to results, which were published by **Pittet et al.**⁽⁵⁾ who reported that PCV13 immunization in 40 NS children is highly immunogenic, regardless of their treatment, and induces high serotype specific IgG titers serum titers over time were similar to those of patients who received the vaccine while their disease was in remission, once they had reached a low-dose steroid therapy. Also our results disagree with **Ulinski et al.**⁽⁶⁾ who documented that serum titers of PPV23 over time were similar between nephrotic patients at onset of disease and those who received the vaccine while their disease was in remission, once they had reached a low-dose steroid therapy.

Concerning the impact of treatment on vaccine responses, there was a highly significant negative correlation between steroid dose at time of vaccination and antibody titer 1 month after vaccination in both groups. In group I; steroid doses at onset of PCV were changed from 30 to 55 mg to 25-40 mg in SRNS subgroup and from 30 to 38 mg to 10-20 mg in SSNS subgroup with significant difference. Fifty percent of nephrotic children within group I (SSNS group) did not receive immunomodulator. On the other hand, 50% in group I was SRNS group; they received pulse methylprednisolone in addition MMF for one case and for other case, one dose IV cyclophosphamide and cyclosporine. Lastly 35% (5 patients) received cyclosporine only. At time of PCV13 in group II, steroid doses at onset, after 1 and 3 M of vaccination were the same doses ranged from 5 to 20 mg. Two patients within group 2 did not receive immunomodulator. On the other hand, cyclophosphamide was used in (4 patients, 40%), MMF (3 patients, 30%) or cyclosporine (1 patients, 10%). As regard therapy at the onset of PCV13 in group II, our results agreed with **Liakou et al.**⁽¹⁴⁾ for PCV13 and disagreed with **Pittet et al.**⁽⁵⁾ for PCV13 response and **Ulinski et al.**⁽⁶⁾ for PPV23 response. They reported that antibody titers over time were similar between nephrotic patients at onset of disease and in remission.

As regard antibody titer over 3 months, there was significant difference between the studied groups regarding trend of antibody at three months which significantly decreased in group II. Our results were surprising; antibody titer in group I raised in 50% (7 case), decreased in 42.9% (6 case) and was steady in 7.1% (1 case). In contrary, 100% (10 cases) of group II it was decreased. Our explanation for increased antibody titer in SRNS in group I maybe because 50% in group I were proteinuric and on pulse methyl prednisolone and other immunomodulatory, also increased weight at time of vaccination and after responding to therapy and stopping proteinuria enhanced immune response. Our results was supported by **Güven et al.**⁽¹⁰⁾ for PPV who reported that most of

NS children may not retain their antibody levels despite a reasonable initial response to the PPV. Disagree with **Pittet *et al.*** ⁽⁵⁾ who reported that the high range were maintained 1 year after immunization. Also, they observed increased long-term protection in children previously immunized by either PPSV or PCV.

CONCLUSION

Nephrotic children in both groups can mount adequate antibody production to pneumococcal vaccine post vaccination, which is equal or higher than 0.35 µg/ml. Nephrotic children who received PCV in remission while on low dose of both oral steroid and immunosuppressive drugs had a high protective antibody titer.

Financial support and sponsorship: Nil.

Conflict of interest: Nil.

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