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ORIGINAL RESEARCH

Humoral Immune Response to SARS-CoV-2 in Children with Idiopathic Nephrotic Syndrome: A Cross-Sectional Exploratory Study

Ibrahim Sandokji[1,2], Sulaiman Abdullah[1], Mohammed Eskembaji[3], Albaraa A Fallatah[4], Maan Hajjar[4], Faten Almutairi[5], Ahmed Arabi Alarabi[5], Mona Hamza Syrafi[5], Mossab Imery[5], Amer Alshengeti[1], Waleed Mahallawi[2,6]

[1]Department of Child and Women's Health, College of Medicine, Taibah University, Madinah, Saudi Arabia; [2]Health and Life Research Center, Taibah University, Madinah, Saudi Arabia; [3]Medical Center, Taibah University, Madinah, Saudi Arabia; [4]Taibah University College of Medicine, Madinah, Saudi Arabia; [5]Maternity and Children Hospital, King Salman bin Abdulaziz Medical City, Madinah, Saudi Arabia; [6]Clinical Laboratory Sciences Department, College of Applied Medical Sciences, Taibah University, Madinah, Saudi Arabia

Correspondence: Ibrahim Sandokji, Department of Child and Women's Health, College of Medicine, Taibah University, Madinah, Saudi Arabia, Email isandokji@gmail.com

Background: Children with idiopathic nephrotic syndrome face a high risk of infections due to an abnormal antibody response. This study aims to evaluate the humoral immunity in children with nephrotic syndrome against SARS-CoV-2.

Methods: This cross-sectional study assessed anti-spike SARS-CoV-2 IgG levels in children with nephrotic syndrome and compared them with those in the control group. Data on COVID-19 exposure and vaccination were collected from caregivers. Statistical analyses were performed using appropriate parametric and non-parametric tests, with a significance level set at $p < 0.05$.

Results: Thirty-five children (10 with nephrotic syndrome and 25 controls) were enrolled. Seropositivity rates were 60% in children with nephrotic syndrome versus 32% in controls ($p = 0.15$). Mean antibody levels were comparable between groups (0.74 ± 0.68 vs 0.89 ± 1.24, $p = 0.64$), with no statistically significant differences observed in children receiving steroid therapy.

Conclusion: The humoral response to COVID-19 was similar in children with idiopathic nephrotic syndrome compared to control children, suggesting that routine vaccination schedules remain appropriate in this group. These findings suggest preserved antibody responses in this population; however, due to the exploratory nature of this study, larger studies are needed before clinical recommendations can be modified.

Keywords: immunology, nephrotic syndrome, pediatric nephrology, SARS-CoV-2

Introduction

Nephrotic syndrome (NS) is a common chronic glomerular disorder in children that causes heavy proteinuria due to podocyte injury.[1,2] NS in children is generally classified into idiopathic, secondary, and inherited forms. Idiopathic NS is the most common (90%) and is primarily caused by minimal change disease.[3] Most children with NS are steroid-sensitive, while a small proportion are steroid-resistant and may require immunosuppressive therapies.[4]

Children with idiopathic NS are at increased risk of infections due to immunosuppressant use and urinary losses of immunoglobulins.[3] Recently, B-cell dysfunction has been considered a key factor in the development of idiopathic NS.[5] Therefore, abnormal antibody responses in children with idiopathic NS may increase the risk of viral infections.[6,7] IgG levels are lower in children with NS during relapses than in remission.[8] However, it has been reported that NS patients produce IgG at levels comparable to healthy subjects in vivo.[9] Additionally, the immunogenicity of the COVID-19 vaccine is well established among NS patients receiving immunosuppressive medications.

During the COVID-19 pandemic, the humoral response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was used as a diagnostic and prognostic tool.[10] SARS-CoV-2 IgM antibodies can be measured 3–6 days after

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symptoms appear and remain for 12 weeks.[11] The SARS-CoV-2 IgG antibody develops 16–18 days after infection and declines by the 14th week, although in some cases it can persist for more than a year.[9] Unlike adult patients, children typically develop only anti-spike IgG antibodies against SARS-CoV-2.[12]

Research shows that many vaccines can generate long-lasting humoral immunity against rubella, mumps, and measles.[13] On the other hand, some viruses, such as seasonal influenza and SARS-CoV-2, cause humoral immune responses that are typically short-lived, lasting less than a year.[14] Although initial antibody responses after vaccination are driven by plasmablasts and short-lived plasma cells, a vaccine's ability to produce long-lived plasma cells is key to establishing durable humoral immunity.[15]

Children infected with COVID-19 may be asymptomatic or present with symptoms such as fever (51.2%) and/or cough (43.5%).[16] Other symptoms include myalgia/weakness (21.7%), headache (21.7%), sore throat (8.9%), nausea/vomiting (6.4%), and diarrhea (6.4%). The COVID-19 pandemic requires the prompt identification of infected individuals using efficient, cost-effective SARS-CoV-2 screening tools to prevent the spread of the virus. The gold standard diagnostic test is reverse transcription-polymerase chain reaction (RT-PCR), which has been used for pediatric patients in Saudi Arabia. An alternative testing method is the Panbio COVID-19 Ag Rapid Test Device (P-RDT), although it has lower sensitivity in children.[17]

There is limited evidence assessing the humoral immune response in children with nephrotic syndrome, despite their higher risk of infection and frequent exposure to immunosuppressive therapy. Understanding how urinary protein loss in nephrotic syndrome impacts this response may provide insight into the interaction between the humoral immune system and systemic disease processes. Therefore, this study aims to evaluate the humoral immune response to SARS-CoV-2 in pediatric patients with nephrotic syndrome compared to controls, and to explore its clinical implications for vaccination and infection risk. We hypothesized that children with idiopathic nephrotic syndrome may exhibit altered humoral immune responses compared to control children due to immunosuppressive therapy and urinary immunoglobulin loss.

Methods

Study Participants and Data Collection

This is a cross-sectional study conducted at the Maternity and Children's Hospital in Madinah, Saudi Arabia. The study recruited children (under 18 years old) with a confirmed NS diagnosis. Controls were hospital patients without nephrotic syndrome, which may introduce variability; however, they were included to reflect a real-world comparison group. Patients aged 18 years or older or with severe anemia were excluded from the study. We documented the participants' vaccination status, including their vaccine regimen and the type of vaccine administered. During the study period, according to the Saudi Ministry of Health, all children were advised to receive a single-dose mRNA vaccine.[18] All vaccinated participants received the Pfizer-BioNTech (BNT162b2) mRNA vaccine.

Sample Collection

The collected samples were centrifuged at 2500 rpm for 10 minutes within one hour of collection. The serum was then separated and stored at −20°C until further analysis. All laboratory testing was conducted at the Virology Research Laboratory, College of Applied Medical Sciences, Taibah University, Saudi Arabia.

Enzyme-Linked Immunosorbent Assays (ELISA)

According to the manufacturer's instructions, anti-SARS-CoV-2 IgG antibodies in the participants' serum were measured using ELISA kits (BGI). Each assay plate contained positive, negative, and blank controls. The test showed a specificity of 98.38% and a sensitivity of 98.71% for IgG detection.

Briefly, serum samples were diluted 1:100 and added to microtiter plates pre-coated with SARS-CoV-2 S1/S2 antigens. Plates were incubated at 37°C for 30 minutes and then washed. A secondary anti-human IgG/IgM antibody conjugated with horseradish peroxidase was added, followed by a 20-minute incubation at 37°C. After a second wash, the substrate solution was added, and the mixture was incubated in the dark for 10 minutes. A stop solution was then applied, and optical density (OD) was measured at 450 nm.

According to the manufacturer's guidelines, samples were classified as positive or negative based on a predefined threshold: samples exceeding the threshold were considered positive, while those below were deemed negative.

Ethical Consideration

Informed consent was obtained from all parents or guardians of participants before enrollment. The study was approved and reviewed by the King Salman bin Abdulaziz Medical City Institutional Review Board (IRB approval number: 22–026). This study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

We performed descriptive analysis to summarize the demographic and clinical characteristics of participants with and without NS. Categorical variables were presented as frequencies and percentages, and comparisons between groups were conducted using Fisher's exact test due to the small sample size. The Shapiro–Wilk test was used to assess the normality of continuous variables. Normally distributed data were expressed as means ± standard deviation (SD) and compared using the independent *t*-test. Non-normally distributed data were reported as medians with interquartile range (IQR) and compared using the Mann–Whitney *U*-test. To evaluate the potential influence of nephrotic status on humoral immune response to COVID-19, we generated a swarm plot to illustrate the distribution of antibody levels across the two groups. When we attempted to assess the effect of immunosuppressive medication on antibody count, we found that the only immunosuppressive regimen used by NS patients was a steroid-based regimen; therefore, we used a drop-line mean plot to assess the combined effect of steroids and nephrotic status on antibody count. These visualizations were selected to demonstrate distribution patterns and emphasize the possible impact of steroid therapy.

A formal sample size calculation was not performed, and the study should be considered exploratory. An alpha level of <0.05 was considered significant. We used SPSS 27 (IBM®, Armonk, NY, USA) for statistical analyses.

Results

We enrolled a total of 35 children: 10 with NS and 25 control children (Table 1). Among the NS group, 80% were boys, with an average age of 8.5 ± 3.92 years. In the non-NS control group, 44% were boys, with a mean age of 5.52 ± 5.01 years. There was no statistically significant difference between the two groups ($p = 0.1$). Significant differences were observed in median height (128 cm for NS vs. 100 cm for non-NS; $p < 0.01$) and mean weight (28.79 ± 15.49 kg for NS and 15.70 ± 12.57 kg for non-NS). However, there was no statistically significant difference in percentiles between the groups.

Table 1 Characteristics of the Study Participants (NS vs Non-NS)

	Total	Non-NS	NS	p-value
Number (%)	35	25 (71)	10 (29)	
Age (years, mean ± SD)	6.4 ± 4.9	5.5 ± 5	8.5 ± 3.9	0.10
Sex (male, n [%])	19 (54.3)	11 (44.0)	8 (80.0)	0.07
Nationality (Saudi, n [%])	26 (74.3)	19 (76)	7 (70)	0.69
Height (cm, median [IQR])	100.00 [125–70]	100 [111–65]	128 [137.2–106.5]	<0.01
Height (percentile, median [IQR])	3.3 [29.8–1]	3.3 [69.49–0.1]	8.99 [20.5–0.3]	0.58
Weight (kg, mean ± SD)	19.4 ± 14.5	15.7 ± 12.6	28.8 ± 15.5	0.01
Weight (percentile, median [IQR])	4 [56.75–0.1]	0.8 [37.5–0.1]	18.5 [84.65–0.5]	0.16
Non-NS disorders	Cardiac disorders	2 (8)		
	Gastrointestinal disorders	3 (12)		
	Hematological disorders	5 (20)		
	Metabolic disorders	4 (16)		
	Kidney disorders	7 (28)		
	Sepsis	3 (12)		
	Respiratory disorders	1 (4)		

(*Continued*)

Table 1 (Continued).

	Total	Non-NS	NS	p-value
NS classification	SSNS		9 (90)	
	SDNS		1 (10)	
Maintenance immunosuppression				
Steroid-based regimen (n [%])	8 (22.9)	2 (8)	6 (60)	<0.01
Exposure to COVID-19				
Proven infection (yes, n [%])	8 (22.9)	5 (20.0)	3 (30)	0.66
History of contact (yes, n [%])	9 (25.7)	5 (20)	4 (40)	0.39
COVID-19 vaccination (yes, n [%])	4	1 (4)	3 (30)	0.06
Serological evaluation				
IgG (OD, mean ± SD)	0.9 ± 1.1	0.9 ± 1.2	0.7 ± 0.7	0.64
Seropositive (yes, n [%])	14 (40)	8 (32)	6 (60)	0.15

Among the NS group, 60% (6 out of 10) were in relapse and receiving steroid therapy, compared to only 8% (2 out of 25) of the non-NS group who were on steroid therapy for other reasons ($p < 0.01$). Additionally, most participants in the NS cohort were infrequently relapsing, steroid-sensitive (9 out of 10), with only one patient who was frequently relapsing, steroid-sensitive, and was receiving mycophenolate. None of the included patients had received other immunosuppressive therapies, such as rituximab. None of the included patients were steroid-resistant.

Seropositivity did not significantly differ between the groups (6, 60% for NS vs 8, 32% for non-NS; $p = 0.15$). Exposure to COVID-19 infection occurred in 3 (30%) NS patients and 5 (20%) non-NS control subjects ($p= 0.66$). There is no statistically significant difference in vaccination status or history of contact between the two groups, as indicated by p-values of 0.06 and 0.39, respectively. All vaccinated children received only a single dose.

As shown in Figure 1, there appears to be a difference in antibody levels between the two groups; however, the *t*-test showed no significant difference (0.74 ± 0.68 NS mean count vs 0.89 ± 1.24 non-NS mean count; $p = 0.64$). A drop-line mean plot (Figure 2) indicated a slight difference between the steroid and non-steroid groups; nonetheless, the *t*-test results found no significant differences (Table 2).

The non-NS group includes children with presenting disorders of the kidney (28%), blood (20%), metabolism (16%), gastrointestinal tract (12%), sepsis (12%), cardiac (8%), and respiratory disorders (4%). Seropositivity did not significantly differ among these diagnoses.

Discussion

In this cross-sectional exploratory study, we observed that the humoral response to COVID-19 in children with nephrotic syndrome is comparable to that of pediatric patients with other conditions. Additionally, steroid therapy was not associated with a statistically significant difference in IgG levels or seropositivity against COVID-19. These findings should be interpreted cautiously, given the exploratory nature of the study and the limited sample size.

Our findings align with a study of children with nephrotic syndrome who received the COVID-19 vaccine and found no effect of immunosuppressive therapy on vaccine-induced IgG antibodies.[19] The absence of a statistically significant effect of steroid therapy on IgG levels may be explained by its beneficial effect on proteinuria, which may reduce urinary immunoglobulin loss. In addition, steroids may influence B-cell dynamics by improving lymphocyte trafficking between the circulation and lymphoid tissues, potentially supporting antibody production.[20]

In children with NS, urinary loss of IgG leads to decreased serum concentrations and an increased fractional catabolic rate, indicating a contributory role of the kidney in IgG breakdown during proteinuric conditions.[21] Recent studies showed that serum IgG and IgA levels are reduced in NS patients, whereas IgM levels are elevated.[11] It has been suggested that the underlying immunological defect in idiopathic nephrotic syndrome involves impaired T-cell function, which disrupts the class-switching process from IgM to IgG. Furthermore, similar to albumin, IgG is lost in the urine,

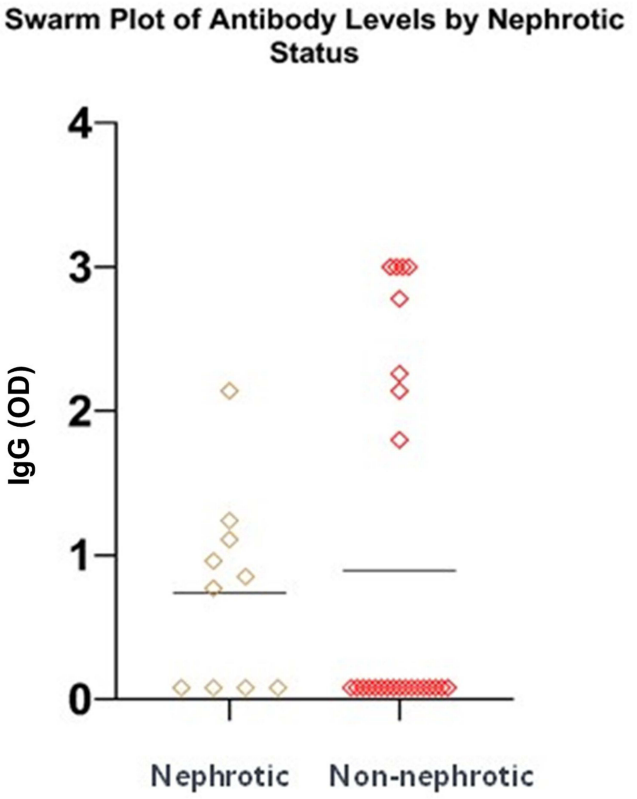

Figure 1 Swarm plot illustrating the distribution of anti–SARS-CoV-2 IgG levels in children with and without nephrotic syndrome. Each point represents an individual participant. Antibody levels are expressed as optical density (OD) values measured at 450 nm. The horizontal line indicates the group mean.

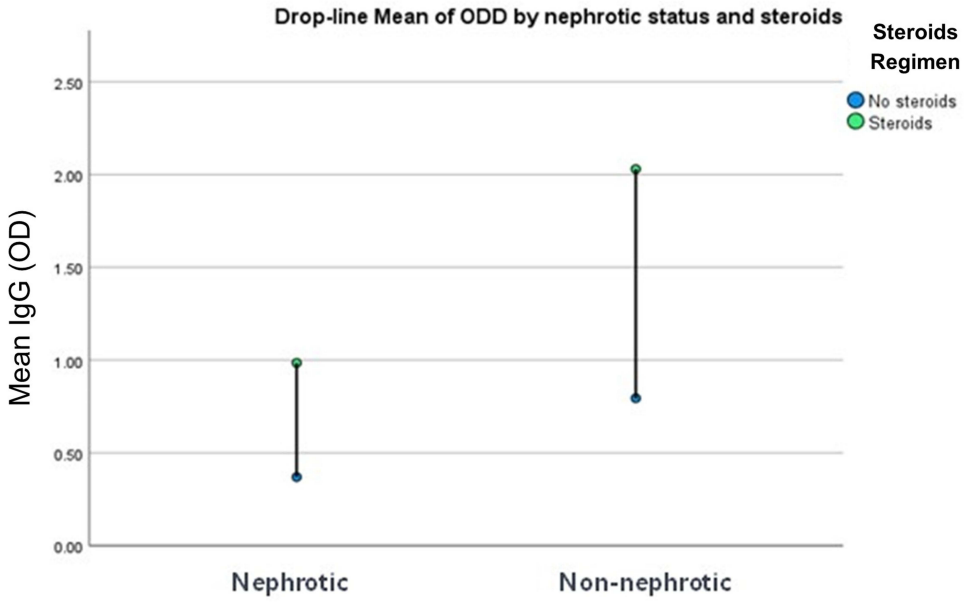

Figure 2 Drop-line plot showing mean anti–SARS-CoV-2 IgG levels according to nephrotic syndrome status and steroid treatment. Antibody levels are expressed as optical density (OD) values measured at 450 nm. Vertical lines represent variability around the mean.

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Table 2 Comparison of Antibody Levels Based on Steroid Use and Nephrotic Syndrome Diagnosis by *t*-Test

	Steroids	No Steroids	p-value
NS	0.99	0.37	0.17
Non-NS	2.03	0.79	0.18
p-value	0.09	0.51	

leading to decreased serum levels and an increased fractional catabolic rate, suggesting a renal contribution to IgG breakdown under proteinuric conditions.[22]

A study was conducted to examine IgG levels in steroid-sensitive NS.[23] The study involved 44 pediatric patients with steroid-sensitive NS, with 14 examined during relapse and 30 during remission. A comparative analysis was performed against a control group of 23 healthy children. In a subgroup of 23 patients (12 in remission and 11 in relapse), a detailed assessment of total IgG, IgM, and IgA levels was conducted. Notably, serum IgM levels showed a statistically significant increase during relapse compared with remission ($p < 0.05$) and with the control group ($p < 0.01$). Similarly, IgA levels were markedly elevated in both relapse states compared with remission and controls ($p < 0.01$ and $p < 0.001$, respectively). Additionally, IgG levels were found to be lower during remission than in controls ($p < 0.03$).[17]

Importantly, our findings align with the absence of significant differences when comparing children with and without NS. While we have identified a potential link between steroid use and seropositivity, it is important to acknowledge several limitations of our study. First, the small sample size has led to unreliable data, reducing the reliability of our conclusions. Second, our cohort study involved only a single vaccine dose, and we did not compare these results with those of individuals who received a full vaccination series. Although differences in height and weight were observed between groups, there was no statistically significant difference in the corresponding percentiles, and these variables were not the primary focus of the present serologic analysis. Detailed information regarding steroid dose and duration was not consistently available. Furthermore, important clinical parameters such as serum creatinine, serum albumin, and quantitative proteinuria were not consistently available and therefore were not included in the analysis. Detailed information regarding steroid dose and duration was not consistently available. The timing between vaccination or infection and antibody measurement was not consistently documented. Additionally, the use of a heterogeneous control group may introduce potential confounding factors that could influence immune responses. Lastly, cellular immunity was not assessed, and longitudinal follow-up was not available. Our findings support the hypothesis that the decrease in IgG is likely related to steroids' role in preventing proteinuria, reinforcing the idea that patients with frequent relapses tend to have lower IgG levels.

Conclusion

In conclusion, our findings indicate that pediatric NS patients do not differ in humoral immunity from non-NS children. However, these findings should be considered exploratory and hypothesis-generating and require confirmation in larger studies before informing clinical recommendations. Until larger studies are conducted, COVID-19 vaccination is recommended on a regular schedule; however, additional doses may not be necessary.

Recommendations

Our findings reassure that children with idiopathic nephrotic syndrome, even those on steroids, can develop humoral responses to SARS-CoV-2 similar to other children. This confirms the safety and effectiveness of COVID-19 vaccination in this at-risk group.

We recommend investigating the immune response to COVID-19 vaccination across different NS subtypes, as well as during relapse, remission, or while taking immunosuppressive medications. We believe long-term longitudinal studies with extended follow-up are necessary to better understand the long-term immune response in children with NS.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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