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Retrospective Study

Nephrotic syndrome in children during the COVID-19 pandemic

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Summary

The COVID-19 pandemic resulted in public health measures and fewer viral infections, which trigger the nephrotic syndrome. Our objectives were to characterize the effect of the COVID-19 pandemic on children with nephrotic syndrome. This single-center retrospective chart review compared children with nephrotic syndrome one year before the pandemic with the first wave of the pandemic. Epidemiologic events, clinical characteristics, and health care utilization were compared using paired t-tests, Fisher's exact tests and Wilcoxon Rank Sum tests. Among 96 children the mean age was 10.7 ± 5.28 years. The distribution was minimal change disease (16.7%), focal segmental glomerulosclerosis (12.5%), membranous nephropathy (1%) and not biopsied (69.8%). Medication responsiveness was steroid-sensitive (25%), frequently relapsed (54%) and steroid-resistant (20.8%). There were 14 new diagnoses of nephrotic syndrome pre-pandemic and 18 during the pandemic. Fewer relapses during the pandemic were likely due to fewer viral illnesses from public health measures during the pandemic.

More Information

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Introduction

SARS-CoV-2, a respiratory virus that led to the COVID-19 global pandemic, was originally detected in China with the first documented case in the U.S. the United States (U.S.) on January 20, 2020. Since then, over 64.3 million adults and 12.1 million children have had documented COVID-19 infections in the U.S [1]. COVID-19 is reported to have a milder course in the healthy pediatric population compared to the adult population, but children with medical co-morbidities such as cardiovascular disease, pulmonary disease, and an immunocompromised state are at greater risk for more severe disease [2,3].

Nephrotic syndrome is known to be closely intertwined with infections, as relapses are often triggered by infectious etiologies [4,5]. Children with nephrotic syndrome are predisposed to infections due to the immunosuppressive agents used for treatment and decreased serum immunoglobulin levels during times of relapse [6]. A recent systematic review including 43 patients with COVID-19 in children with idiopathic nephrotic syndrome concluded that children with nephrotic syndrome are not at higher risk for SARS-CoV-2 infection, but relapses triggered by COVID-19 are possible [7]. Due to public health measures such as masking, social distancing, and school closures during the COVID-19 pandemic, there were also fewer non-COVID 19 respiratory infections [3]. There is little known about the effect of the COVID-19 pandemic on the epidemiology, clinical patient characteristics and health care utilization practices in children with nephrotic syndrome during the COVID-19 pandemic.

The purpose of this study was to characterize the effect of COVID-19 on children with nephrotic syndrome at a tertiary children's hospital in New York during the first year of the pandemic, compared to the year prior. Specifically, the aim was to understand whether there were changes in the epidemiology (incidence of new diagnoses and number of relapses), clinical characteristics (adiposity, blood pressure, lab values) and health care utilization (in-person visits, telemedicine visits, emergency department [ED] visits, hospitalizations) of pediatric patients with nephrotic syndrome. We hypothesized that the COVID-19 pandemic led to a decreased incidence of new diagnoses and number of relapses, increased body mass index (BMI) and blood pressure, decreased vitamin D level and decreased number of ED visits and hospitalizations when compared to the pre-pandemic period.

Methods

This was a retrospective chart review of patients with nephrotic syndrome followed at Cohen Children's Medical Center in New Hyde Park, New York. Based on the epidemiology of COVID-19 in New York, the pre-pandemic period was defined as March 1, 2019, to February 28, 2020. The first year of the pandemic from March 1, 2020, to February 28, 2021, was defined as the pandemic period, based on the start of the lockdown period in New York. During this time, there was a period of shelter in place, social distancing and virtual education in the New York metropolitan area [8]. Children and adolescents < 21 years followed by pediatric nephrology with a diagnosis of idiopathic nephrotic syndrome, including minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and membranous nephropathy (MN) were included in the study. Children with kidney transplants and those who were dependent on dialysis were excluded. Data were collected by a combination of extraction from the electronic medical record (AllScripts and Sunrise Clinical Manager) using ICD-10 codes (N04.9, N04. 1, 581.3 , N04.2) and manual chart review. The study was approved by the Northwell Health Institutional Review Board.

Study outcomes

The primary outcomes of interest were the epidemiology, patient clinical characteristics and health care utilization of children with nephrotic syndrome during the pandemic period compared to the pre-pandemic period.

Epidemiology outcomes included the number of new diagnoses of nephrotic syndrome/year and the number of relapses per patient/year. A patient was considered to be in relapse based on parent reports from at-home testing or identification of relapse by a healthcare provider.

Clinical characteristic outcomes included BMI z-scores, blood pressure, serum vitamin D levels, estimated glomerular filtration rate (eGFR) and first-morning urine protein: creatinine ratio (UPC). Blood pressure was obtained from clinic visits using an oscillometric device. Systolic and diastolic blood pressures were indexed to the 95th percentile for age, sex and height [9]. eGFR was calculated using the bedside Schwartz equation [10].

Healthcare utilization metrics included the number of in-person office visits/year, telehealth visits/year, ED visits/year and hospitalizations/year.

Demographic characteristics included age, self-reported race and ethnicity and type of nephrotic syndrome diagnosis. Classification of nephrotic syndrome included biopsy-proven MCD, FSGS, MN and unspecified/non-biopsied nephrotic syndrome. Patients were categorized as steroid sensitive, frequent relapsing and steroid-resistant based on physician assessment documented in the clinical record.

Statistical analysis

Demographic and clinical characteristics were described using means with standard deviations, frequencies and proportions. Paired t-tests or Wilcoxon Rank Sum test was used, as applicable, to compare variables before and during the pandemic. Analyses were limited to patients who were followed for nephrotic syndrome during the pre-pandemic and first wave of the pandemic periods. The incidence of new nephrotic syndrome diagnoses (new diagnoses divided by the number of new patients per year) were compared pre-pandemic to the first wave via a Fisher's exact test. New diagnoses in the pandemic period were not included beyond initial demographic data and comparing new diagnoses to effectively compare pre and post-pandemic groups with sufficient data for each time period. Analyses were stratified by sub-group of steroid-sensitive/frequent relapsing and steroid-resistant nephrotic syndrome. SPSS 26 (IBM Inc.) was the statistical software package used. $p < 0.05$ was the criterion used for statistical significance.

Results

Among 96 children followed both pre-pandemic and during-pandemic, the mean age was 10.7 ± 5.28 years, 64.6% were male and 14.6% identified as Black. Diagnoses included: 16.7% MCD, 12.5% FSGS, 1% MN and 69.8% unspecified/not biopsied nephrotic syndrome. Nephrotic syndrome classification was as follows: 25% of patients were steroid sensitive, 54% were frequently relapsing and 20.8% were steroid resistant (Table 1).

Among the children with steroid-sensitive/frequently relapsing nephrotic syndrome, there were a significantly higher number of relapses pre-pandemic (1.27 ± 1.53) compared to during the first wave of the pandemic (0.59 ± 0.95), $p < 0.001$ (Table 2). However, there was no difference in the number of relapses in the steroid-resistant patients

Table 1: Demographics and Clinical Characteristics.

Characteristic	*n* = 96
Age (years)	10.7 ± 5.28
Male	64.6% (*n* = 62)
Race:	
White	20.8% (*n* = 20)
Black	14.6% (*n* = 14)
Asian	24.0% (*n* = 23)
Other	40.6% (*n* = 39)
Ethnicity: Hispanic	12.5% (*n* = 12)
Diagnosis:	
MN	1% (*n* = 1)
MCD (biopsy)	16.7% (*n* = 16)
FSGS	12.5% (*n* = 12)
Unspecified/not biopsied	69.8% (*n* = 67)
Classification:	
Steroid Responsive	25.0% (*n* = 24)
Frequent Relapses	54% (*n* = 52)
Steroid Resistant	20.8% (*n* = 20)

MN: Membranonephritis; MCD: Minimal Change Disease; FSGS: Focal Segmental Glomerulosclerosis

(Table 3). There were 14 new diagnoses of nephrotic syndrome pre-pandemic (829 new patients total) and 18 new diagnoses during the pandemic (699 new patients total). There was no statistically significant difference in the incidence of new nephrotic patients (pre-pandemic 1.69% vs. pandemic 2.57%, p = 0.28). COVID-19 infection was associated with new nephrotic syndrome diagnoses in two patients.

When comparing overall clinical characteristics pre-pandemic and during the pandemic, the mean systolic blood pressure index was significantly lower during the pandemic (0.74 ± 0.27) compared to pre-pandemic (0.84 ± 0.20), p = 0.012. There were no significant differences in BMI Z-score, vitamin D, eGFR, or UPC (Table 4). In steroid sensitive/frequent relapsing patients, the SBP indices [pre-pandemic (0.83 ± 0.34), during the pandemic (0.71 ± 0.43), p = 0.002] and DBP indices [pre-pandemic (0.88 ± 0.54), during the pandemic (0.77 ± 0.57), p = 0.041] were lower during compared to pre-pandemic. In patients with steroid-resistant nephrotic syndrome, similar trends were seen (Table 3). There were no significant differences in BMI Z-score, vitamin D, eGFR, or UPC in either group (Tables 2,3).

Regarding healthcare utilization, there were fewer in-person office visits during the pandemic (2.28 ± 2.13) compared to pre-pandemic (3.03 ± 2.24), p < 0.001, and more telehealth visits during the pandemic (0.71 ± 0.97) compared to pre-pandemic (0.00 ± 0.00), p < 0.001. There were fewer ED visits during the pandemic (0.19 ± 0.51) compared to pre-pandemic (0.63 ± 0.11), p < 0.001. There were also fewer hospitalizations for nephrotic syndrome during the pandemic (0.05 ± 0.27) compared to pre-pandemic (0.25 ± 0.62), p = 0.003. Similar results were seen for the steroid-responsive/frequently relapsing group (Table 2). For the steroid-resistant group, similar results were also seen with the exception that there was no difference in the number of in-person visits pre-pandemic and post-pandemic (Table 3).

Table 2: Patients with nephrotic syndrome who are steroid responsive + frequently relapsing.

Marker (Mean)	Pre-COVID-19 Pandemic	During-COVID-19 Pandemic	p value (2-tailed t test)
Last BMI Z-Score (mean)	0.60 ± 1.36	0.53 ± 1.08	0.67
Mean SBP Index	0.83 ± 0.34	0.71 ± 0.43	0.002
Mean DBP Index	0.88 ± 0.54	0.77 ± 0.57	0.041
Mean Vitamin D (ng/dL)	19.11 ± 10.11	20.04 ± 13.15	0.78
Mean eGFR	139.7 ± 41.00	138.0 ± 42.11	0.08
Mean UPC	4.36 ± 12.64	1.79 ± 2.81	0.071
Number of Relapses	1.27 ± 1.53	0.59 ± 095	< 0.001
Number of ED visits	0.49 ± 0.90	0.18 ± 0.49	0.017
Number of hospitalizations	0.15 ± 0.39	0.04 ± 0.19	0.045
Number of In- Person Office Visits	2.66 ± 1.79	2.04 ± 2.07	0.012
Number of Telehealth isits	0 ± 0.00	0.64 ± 0.85	< 0.001

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; eGFR: estimated GFR, UPC: Urine Protein/Creatinine.

Table 3: Patients with nephrotic syndrome who are steroid resistant.

Marker (Mean)	Pre-COVID-19 Pandemic	During-COVID-19 Pandemic	p value (2-tailed t test)
Last BMI Z-Score (mean)	0.45 ± 1.51	0.61 ± 1.29	0.378
Mean SBP Index	0.85 ± 0.30	0.61 ± 0.44	0.00
Mean DBP Index	0.83 ± 0.43	0.67 ± 0.52	0.01
Mean Vitamin D (ng/dL)	19.93 ± 9.76	19.51 ± 12.96	0.892
Mean eGFR	131.57 ± 39.43	131.54 ± 39.92	0.997
Mean UPC	2.78 ± 5.52	2.24 ± 3.53	0.460
Number of Relapses	0.52 ± 1.16	0.19 ± 0.60	0.393
Number of ED visits	1.14 ± 1.59	0.19 ± 0.60	0.016
Number of hospitalizations	0.62 ± 1.02	0.09 ± 0.44	0.024
Number of In- Person Office Visits	4.24 ± 3.22	3.33 ± 2.24	0.158
Number of Telehealth Visits	0 ± 0.00	1.10 ± 1.37	0.002

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; eGFR: estimated GFR, UPC: Urine Protein/Creatinine.

Table 4: Nephrotic Syndrome Measurements, Lab Values and Healthcare Utilization (diagnosed prior to March 2020).

Marker	Pre-COVID-19 Pandemic	During-COVID-19 Pandemic	p value (2-tailed t-test)
Last BMI Z-score (mean)	0.70 ± 4.72	0.43 ± 1.24	0.086
Mean SBP Index	0.84 ± 0.20	0.74 ± 0.27	0.012
Mean DBP Index	0.86 ± 0.34	0.78 ± 0.35	0.076
Mean Vitamin D (ng/mL)	20.56 ± 4.72	20.90 ± 5.47	0.762
Mean eGFR	134.10 ± 42.41	120.64 ± 40.28	0.500
Mean UPC	3.70 ±6.54	3.92 ± 9.94	0.143
Number of Relapses	0.93 ± 1.42	0.56 ± 0.94	0.003
Number of ED visits	0.63 ± 1.11	0.19 ± 0.51	< 0.001
Number of hospitalizations	0.25 ± 0.62	0.05 ± 0.27	0.003
Number of In- Person Office Visits	3.03 0 ± 2.24	2.28 ± 2.13	< 0.001
Number of Telehealth Visits	0 ± 0.00	0.71 ± 0.97	< 0.001

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; eGFR: estimated GFR, UPC: Urine Protein/Creatinine.

Discussion

In this single-center study of children with nephrotic syndrome, there were changes in the epidemiology, clinical characteristics, and health care utilization of children with nephrotic syndrome during the first wave of the pandemic compared to the pre-pandemic year. Specifically, there were significantly fewer nephrotic syndrome relapses during the pandemic. Systolic blood pressure was higher pre-pandemic compared to during the pandemic. Additionally, as would be expected, there were fewer in-person office visits, ED visits and hospitalizations during the pandemic period compared to the pre-pandemic. Finally, there was a shift in access to care since the introduction of telehealth utilization for routine visits for children with nephrotic syndrome.

There were significantly fewer relapses during the pandemic compared to pre-pandemic in our cohort. Similar trends were found in shorter periods (months) with clinically fewer relapses during the COVID-19 pandemic; however, these studies did not show statistical significance in these findings [11]. Our findings are thought to be explained by the fact that social distancing likely led to fewer viral infections and therefore fewer nephrotic syndrome relapses. There were also fewer non-COVID viral illnesses transmitted globally. The etiology of this overall trend is likely due to public health measures such as social distancing, mask-wearing, virtual education and remote work during the pandemic [12-14]. There is a known association between viral illnesses as triggers nephrotic syndrome relapses. Proposed mechanisms are that increased immune complexes involving viral antigens vs proinflammatory factors inducing immune responses in children with viral syndromes trigger nephrotic syndrome relapses [15].

The new number of diagnoses during the pandemic was not significantly different compared to the year prior. The calculated incidence of new diagnoses was likely overestimated during the pandemic period due to the decrease in the referral of new patients during this time, however, results would still be similar if the referral pattern was unchanged. As seen with the two patients in this cohort, there have been some cases of COVID-19 triggering a new diagnosis of nephrotic syndrome reported in the literature [16,17].

Systolic blood pressure was higher pre-pandemic compared to post-pandemic. However, the difference in BMI z-scores was not statistically significant. Therefore, it is unlikely that this change is due to a difference in weight or lifestyle. One possible explanation for this improvement is that due to fewer nephrotic syndrome relapses, fewer steroid courses were prescribed. This could have resulted in lower systolic and diastolic blood pressures during the pandemic [18].

In-person health care utilization overall was significantly lower in the pandemic period compared to the pre-pandemic period. This same trend was seen across the country in all age groups when social distancing was at its peak [19,20]. This finding was more noteworthy in children compared to adults when examining ED visits for all illnesses, including COVID [21]. Considering this information in combination with fewer nephrotic syndrome relapses leads us to conclude that there were potentially fewer virally induced relapses in the pandemic period.

While there was less in-person healthcare utilization, the widespread use of telehealth began during the pandemic in children with nephrotic syndrome. This is consistent with the trends seen nationally among all ages as multiple other centers worked to adapt during the COVID-19 pandemic [22]. It is likely that our health system, similar to many other health systems nationwide, will continue to utilize telehealth. However, as this rise in telehealth was most noteworthy in high-income countries [23], this shift must continue with caution and in consideration of those with limited access to technology resources [24].

One limitation of this study is the follow-up time of one year. There are also varying degrees of social distancing which we could not evaluate objectively due to the retrospective nature of the study. Additionally, the fluctuations in variants and the introduction of vaccinations were not considered in our timeframe. Another limitation is that these findings were limited to one children's hospital in New York and changes in epidemiology could have been due to shifts in referral patterns. Additionally, this was an electronic medical record study, so some potentially useful data such as family economic status, number of family members and ability to social distance were not collected. However, this information would have been valuable to determine the effect of adherence to national recommendations for social distancing and hygiene-affected relapses.

Overall, we propose that resources should continue to be allocated to develop telehealth, as it was utilized heavily during the pandemic and will likely continue to be used. Reasonable social distancing measures such as hand washing and mask-wearing should continue in patients not only with the nephrotic syndrome but also with any upper respiratory infection symptoms to minimize relapses. However, these implications may not be extrapolated linearly into the future as more factors are introduced, such as vaccination status. In the future, as vaccinations in children continue to evolve, it would be interesting to continue to follow these patients for an additional year to assess the role of vaccinations in rates of relapses.

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