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Long-term Outcome of Childhood Steroid-Sensitive Nephrotic Syndrome

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Abstract

The long-term outcome of childhood steroid-sensitive nephrotic syndrome (SSNS) needs further evaluation. In this study, In this study, we report the long-term outcome of childhood SSNS at our center. Patients and Methods: This is a retrospective review of cohort of children with SSNS followed by cross-sectional follow-up evaluation. We included all children aged ≥16 years with a history of childhood SSNS. Of 45 children diagnosed with SSNS and contacted for follow-up, only 9 children were available for evaluation of long-term outcome. Demographic, socioeconomic, and disease history data were collected through a questionnaire. All the patients were examined and had their urine and blood samples collected for investigations. The data were analyzed using SPSS. Results: The mean age at onset for the 45 children was 7.3 ± 3.9 years. Follow-up revealed that 65.1% had frequent relapsing or steroid-dependent nephrotic syndrome and 34.9% had infrequent relapses. Of nine patients were included in the follow-up study for a median (range) duration of 11 (5–18) years, 2 of the patients were relapsing at the time of the study and two had one or more relapses during the previous year. Estimated glomerular filtration rate (eGFR) declined in two children and the mean eGFR for the whole group was lower at the time of last follow-up than at baseline (P = 0.032). Conclusion: Children with SSNS need careful long-term monitoring of disease activity and kidney function. A larger prospective study is required.

Keywords: Pediatric, long-term, minimal change disease, focal segmental glomerulosclerosis

Introduction

Childhood idiopathic nephrotic syndrome (NS) is chief steroid responsive.[1-4] However, most affected children experience relapses and a considerable percentage develops a troublesome disease course characterized by frequent relapses or steroid dependent pattern.[5] These observations might vary among children from differing ethnic backgrounds. While steroid sensitive NS (SSNS) is more common in Asian children, relapses were reported to be more frequent among Caucasian children.[6] Recent long-term studies showed that the prognosis of SSNS is not as good[7-11] as it was reported before.[12] Esfahani et al. from Iran reported that more than one-third of children with SSNS experience frequent relapses, which continued to adulthood despite the combination of multiple immunosuppressive medications.[7] This is

similar to a report by Fakhouri et al. who found that more than 40% of SSNS patients experience relapses in adulthood.[8] The complications and outcomes of long-term SNSS remain largely unknown for patients from the middle East due to limited number of region specific studies. This is a retrospective review of cohort of children with SSNS, including cross-sectional follow-up, that evaluated the long-term outcome of these children.

PATIENTS AND METHODS

Based on computerized records, we identified all children who fulfilled the following inclusion criteria: diagnosed with SSNS, born before 2001 (aged 16 or older at the time of assessment), followed up at our center and with normal kidney function at the time of SSNS diagnosis. Children with syndromic disease or congenital NS were excluded. Ethical approval was obtained from the Biomedical Ethics Research Committee of the Faculty of Medicine at King Abdulaziz University and written informed consent was obtained from the participants. The study adhered to the principles of the Declaration of Helsinki. Forty-five children fulfilled the inclusion criteria and were contacted for reassessment; however, only nine children were available to be re-evaluated. The reasons for non-availability were various, including change of contact information or expatriates returning to their country of origin.

DATA COLLECTION

We prepared a structured questionnaire, which included questions regarding demographic data, age at diagnosis of SSNS, age at last relapse, age at menarche or puberty, medications received, medication adverse effects, and renal biopsy status. The data were obtained and recorded by a trained researcher. NS was defined as urine protein excretion >40 mg/m2/hr and hypoalbuminemia

(serum albumin <2.5 g/L). Remission of NS was characterized by urine protein excretion reduction to normal level, (i.e., <4 mg/m2/hr or albumin dipstick of nil for three consecutive days), edema resolution, and serum albumin level normalization. SSNS was defined as patients who exhibited remission in response to prednisolone within 4 weeks. A relapse was determined by 300 mg/dl on urine dipstick for 3 consecutive days. Body mass index (BMI) was calculated using the equation: weight/height2 (kg/cm2). Laboratory examinations were requested, including urine analysis and blood tests for serum albumin, renal function, bone profile, parathyroid hormone, and 25-hydroxy vitamin D3 level. In addition, hand X-ray was performed to determine bone age. Estimated glomerular filtration rate (eGFR) was calculated at assessment and presentation using the modified Schwartz formula.[13]

Statistical analysis

Data were analyzed using the IBM SPSS statistical for window (IBM Corp. Released 2012; version 21.0 Armonk, NY). Continuous data are represented as the mean ± standard deviation (SD) whereas categorical data are presented as percentages. Significance between steroid sensitivity and some variables was determined using

the chi-square test for categorical data, and the t-test for continuous variables. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

Baseline data were collected for 45 children, of which only 9 (15.6%) were available for follow-up data. Of the 45 children, 26 (57.8%) were male [Table 1]. The mean age at presentation was 7.3 ± 3.9 years (median, 6 years). Table 1 shows various parameters at baseline, including the mean height, height SD score and eGFR. More than half of the children 26 (57.8%) were Saudi, and most were of Middle Eastern ethnicity (n = 38; 86.4%). Five children (11.4%) were from African origin, and one child (2.3%) was Asian.

Course of nephrotic syndrome

Records were available for 45 patients at baseline [Table 1]. Of these, frequent relapses or steroid-dependent NS pattern was the disease course in 30 (65.1%) patients, while 15 (34.9%) had infrequent relapses. Only nine patients (15.5%) were available for follow-up, whereas the remaining cases (n = 38; 84.4%) were to lost to follow-up. The former were followed up for a median (range) duration of 11 (5–18) years. Two of the nine patients who had follow-up were identified to be in relapse at the time of re-evaluation; these patients had proteinuria, with a urine albumin/creatinine ratio >300 mg/g and hypoalbuminemia of <25 g/L. Another two patients had experienced relapses within the last year, i.e., a total of four patients had active disease. The remaining five patients did not have relapse for more than 1 year at last follow up. The mean height at the time of the evaluation was 158.00 ± 9.35 cm at a median age of 18 years. The mean eGFR was significantly lower (P = 0.032) and mean serum creatinine was insignificantly higher than at baseline [Table 2]; two patients had low eGFR of 80.73 and 60 ml/ min/1.73 m2. The two children with low eGFR were treated with both - cyclosporine and angiotensin-converting enzyme inhibitor. These patients had normal serum calcium of 2.2 ± 0.14 mmol/L (2.1–2.6) and phosphate 1.1 ± 0.4 mmol/L (0.85–1.2) levels All nine children had low vitamin D level with mean ± SD of 20.1 ± 14.2 ng/ml (75–125) and low serum albumin of 30.8 ± 9.9 g/L (35–45). Seven children had no proteinuria while two children had nephrotic range proteinuria at re-evaluation. Eight of them required the use of other immunosuppression medications during their illness.

Discussion

We have observed that more than 40% of patients with SSNS had active disease at early adulthood. This is similar to previous reports of disease activity in 30%–40% of patients approaching adulthood. [7,8] However, a lower proportion of relapses have been reported by other authors. Skrzypczyk et al.,[11] observed relapses in 13.5% of their patients. Fakhouri et al.,[8] observed that the activity of childhood SSNS at adulthood was associated with the age at onset, with younger age at presentation associated with a higher risk of relapse during adulthood. Similarly, severe disease and multiple relapses requiring immunosuppression during childhood were associated with a higher risk of relapse during adulthood. The present study showed that 57.8% of the patients were boys. Similarly, other studies found a male predominance among young children with the disease.[3,14] In our report, the mean age of the patients was 7.3 ± 3.9 years, which is consistent with the results of Alhassan et al.,[3] who found that the mean age of children with SSNS in the AlJouf region of Saudi Arabia was 6.4 ± 3.4 years. A study conducted in France reported onset age at 4.1 years.[1] Previous studies have also observed that patients with early age at onset of NS were more likely to be show steroid sensitive disease course than those who develop the disease at a later age.[15], The increase in serum creatinine during follow up in our patients may have been confounded by increasing muscle mass with age. However, eGFR in children with SSNS is expected to be normal at presentation and stay stable during follow-up.[16] Two children in our study had eGFR below normal, which could be due to prolonged use of cyclosporine. Height SD score was much lower at re-evaluation compared with the value at presentation. The difference did not reach significance, possibly because of small number of children studied. Reduced height velocity could be explained by excessive use of steroids in those children.[17] The low 25-hydroxy vitamin D level in all nine patients, with a median of 17 ng/mL (mean ± SD, 20.1 ± 14.2 ng/mL), is consistent with regional findings.[18,19] There are several limitations in our study, including small number of studied children at a single center and a high rate of attrition, which may have resulted in selective reporting of patients at with severe disease during follow up. We have evaluated only kidney function and disease activity of NS, but did not look at immunosuppression related side effects such as bone health, cataract, fertility and psycho-social parameters such as educational, employment, and marital status.

CONCLUSION

Long-term follow-up is recommended in children with SSNS. Larger studies with prolonged follow up and low attrition rates are needed to investigate the long-term effects of SSNS on renal function and disease activity.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Epidemiology of Pediatric Acute Kidney Injury in the Kingdom of Saudi Arabia

Studies assessing the epidemiology of pediatric AKI vary in their use of standardized definitions. AKI was observed in 37.4% of critically ill children in a recent multicenter prospective cohort study from KSA using the KDIGO definition for AKI.[9] While this incidence is higher than in the AWARE study,[1] it is comparable to a single-center retrospective study from north India that reported AKI in 36.3% of children admitted to PICU,[10] and lower than in recent studies from India reporting AKI in 42.9% critically ill patients using pRIFLE criteria[11] and in 53.2% cases using AKIN definition.[12] The incidence of AKI is higher after cardiac surgery in children receiving extracorporeal membrane oxygenation (ECMO), with a study from King Faisal Specialist Hospital reporting AKI in 90% of 59 children initiated on ECMO.[13] Most children were in failure stage of pRIFLE staging, in contrast to previous studies that have usually reported mild stages of AKI, namely the risk stage of pRIFLE and Stage I of KDIGO criteria.[1,4-6], been a recent expansion of the reports of AKI following cardiac surgery with an expansion of the number of pediatric cardiac surgical centers across the country.[4,8,15] AKI has

also been attributed to other causes, including hemolytic uremic syndrome,[16] vancomycin toxicity,[17] or congenital chloride diarrhea.[18]

RISK FACTORS FOR ACUTE KIDNEY INJURY

Patients with high Pediatric Risk of Mortality (PRISM) score, an index that is known to predict mortality, are at higher risk of AKI. [4,5] Similarly, the incidence of AKI is higher in pediatric patients who require ventilatory support than those who do not.[4,5]

MORTALITY AND ACUTE KIDNEY INJURY

AKI is associated with increased risk of mortality.[1,4,5,15] Advanced stages of AKI are associated with higher likelihood of death.[1,4,5] Oliguric children are at increased risk of dying as compared to those with nonoliguric AKI.[1,4] Other predictors of mortality include volume overload, need for mechanical ventilation, and the requirement of renal replacement therapy (RRT).[5] Hypotension as the etiology of AKI was reported to increase the risk of death 10-fold compared to patients without hypotension.[3] The AWARE study showed that the need for vasoactive support was the strongest predictor of mortality by day 28 after admission, followed by requirement of RRT.[1]

RENAL REPLACEMENT THERAPY

Safder et al. showed that RRT was required in 11.4% of pediatric patients with AKI.[19] In contrast, RRT was required by only 1.5% of children with AKI in the AWARE study.[1] The proportion of pediatric patients requiring RRT was 2.9% (0%–8.6%) of 129,809 admissions to PICU at 30 of 33 centers in the United Kingdom.[20] Peritoneal dialysis (PD), used in 70.7% of the children, and was the most common modality of RRT, followed by continuous RRT (CRRT) which was used in 17.2% patients.[19] Hemodialysis (HD) was used in 8.6% patients, while 3% cases underwent both PD and HD.[19] CRRT was reported to be associated with mortality of 50% in a single-center Saudi study,[21] which is higher than reported elsewhere.[22]

LONG-TERM OUTCOME OF ACUTE KIDNEY INJURY

AKI is associated with increased mortality after discharge from the hospital. The 2-year mortality was reported to be more than 40% in children admitted to the PICU of King Abdulaziz University.[23] The chief predictors of mortality were the severity of AKI and the PRISM score, which increased the risk of mortality by 6% per unit increment in PRISM score.[23] A significant proportion of the survivors had evidence of chronic kidney disease, in the form of reduced estimated glomerular filtration rate, proteinuria, or hypertension.[15,23] This is similar to findings in reports from other parts of the world.[24,25]

ACUTE KIDNEY INJURY IN NEONATES

AKI is common in neonates admitted to the neonatal intensive care unit (NICU). AKI is associated with increased morbidity and mortality and a high long-term risk of chronic kidney disease.[26] A recent study from King Abdulaziz University reported AKI in 56% in NICU admissions. This is much higher than in a previous report from King Khalid University around three decades ago of 3.6%.[27] AKI is more common among low-birth-weight babies and in those born premature.[26,27] Perinatal asphyxia is a major risk factor for AKI in neonates.[26] A high clinical risk index for babies II score predicts AKI in infants with gestational age <32 weeks.[26] Neonatal AKI is shown to be associated with increased mortality.[26,27] However, the rates of mortality in neonates with AKI have decreased to 28.5% compared to 77% around three decades ago.[26,27]

NEW ACUTE KIDNEY INJURY

biomarKers Serum creatinine is a suboptimal biomarker of kidney function, as the rise in serum creatinine is significantly delayed to 48–72 h after an insult and requires loss of function to about 50% before it is reflected in a rise in serum creatinine.[28] Various plasma and urinary biomarkers such as kidney injury molecule-1, neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18, and cystatin C have been proposed and investigated for their role in enabling early detection of kidney injury.[28] There are few Saudi studies to investigate these biomarkers in critically ill pediatric patients. Serum cystatin C was identified as a sensitive, but not a specific, marker for the diagnosis of AKI in critically ill children.[29] Similarly, urinary NGAL (uNGAL) was shown to predict AKI early in critically ill children. [30]

CONCLUSION

AKI is common in critically ill children and neonates. It is associated with increased mortality and length of hospital stay. The severity of AKI is associated with increased inhospital mortality as well as high mortality after discharge, particularly in the early months after admission to PICU. Considerable proportion of survivors develops evidence of chronic kidney disease. Cystatin C and uNGAL are useful in enabling early diagnosis of AKI in critically ill children.

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