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Early Detection of Neonatal Kidney Disease in High Risk Neonates Admitted to Neonatal Intensive Care Unit

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Abstract: This work conducted to study the pattern of different kidney disorders in the NICU, Cairo University during a period of one year. Also, to investigate the role of cystatin C and B2 microglobulin as biomarker in the diagnosis and monitoring of renal diseases. This study included 80 neonates with different patterns of renal disorder. Inclusion criteria were: acute renal injury, proteinuria, hematuria and UTI. The neonates were subjected to history taking and clinical examination. Laboratory investigations will be monitored at day 0, day 4 and on discharge by: CBC, serum sodium, potassium, phosphorus, BUN, creatinine, serum cystatine C and B2 microglobulin. Results: total number of admitted cases was 1143 neonates, signs or laboratory findings suggestive of kidney involvement were present in 6.8% of them, AKI represent 49.8% cases. The commonest cause of AKI was sepsis (72.5%). Initial serum cystatine C and B2 microglobulin revealed no difference while at day 4 and on discharge there was significant difference between AKI and non AKI group ($P<0.05$). On admission serum cystatine C and creatinine revealed no difference while the difference at day 4 was significantly higher in the AKI group, on discharge there was no difference. Conclusion: Although renal insult in babies admitted to NICU had a low prevalence it contributed to mortality of 30%, AKI was the most common cause of kidney affection. Serum cystatine-C and B2 microglobulin may be considered as sensitive predictive parameters for reduced glomerular filteration rate. It is of value for the laboratory diagnosis of AKI.

Key words: Acute Kidney Injury · Cystatine C · B2 Microglobulin · Neonates

INTRODUCTION

Renal disorders are a heterogeneous group of congenital and acquired conditions [1]. In a full term neonate, the kidney functions are not fully mature and functional maturation continues in the postnatal age. Under normal circumstances, the kidney adapt to various endogenous and exogenous stresses, However, in sick neonates and stressful conditions like sepsis and shock the adaptive capacities of the kidney may be overcome leading for renal dysfunction [2].

Acute Kidney Injury (AKI) in the newborn is a common problem in 1the neonatal intensive care unit, the incidence of acute renal failure ranges from (6-24%) [3]. The diagnosis of AKI is usually based on either an evaluation of serum creatinine or the detection of oliguria [4]. However serum creatinine is a poor marker of early renal dysfunction because serum concentration is greatly influenced by numerous non renal factors such as body weight, race, age and total body volume [5].

The utility of serum creatinine is worse in AKI because the patients are not in steady state; hence serum creatinine lags far behind renal injury. Thus substantial rises in serum creatinine are often not witnessed until 48-72 hours [6].

The American Society of Nephrology has designated the development of biomarkers for early detection of AKI as a research priority [7]. Biomarkers are currently being explored to differentiate between different causes of established AKI and to prognosticate outcomes. Currently, the most promising early non-invasive biomarkers of AKI are cystatin-C and B-2 microglobulin [8, 9].

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Aim of the Work: This work is conducted to study the pattern of different kidney disorders among all admissions to the neonatal intensive care units (NICU), Children's Hospital, Cairo University (A tertiary referral care center in Cairo), during the period of one year. Also, to Investigate the role of cystatin C and Beta-2 microglobulin as biomarkers, both for better diagnosis and monitoring of renal diseases.

MATERIALS AND METHODS

This study included 80 neonates (52 males and 28 females) who presented with different patterns of renal disorders that were admitted to Neonatal Intensive Care Unit of Almonira Pediatric Hospital-Cairo University from April 2011 to March 2012.

As regard the gestational age 49 were full term babies more than37 wks and 31 were premature less than 37 wks. Parental consent for all neonates was obtained according to form approved by the Ethics Committee of the National Research Center (NRC).

Inclusions criteria were: acute renal injury, (Oliguria, elevated renal functions and volume overload), elevated blood pressure, proteinuria, hematuria, urinary tract infection, tubular disorders and cystic disease of the kidney.

Study Population

- **Clinical Assessment:** All neonates were subjected to the following:

Full History Taking Stressing On:

- Maternal history (History of recurrent abortions, Mode of delivery focusing on Fetal distress, perinatal asphyxia and Maternal illnesses e.g., infections, drug administrations and Oligohydramnios that may indicate a decrease in fetal urine production.
- Neonatal history (Dietary history, Urine output in 24 hours, urine color and Vomiting)
- Family history of similar problems and Consanguinity

Detailed clinical examination including anthropometric measurements, general examination and systemic examination focusing on abdominal examination.

- **Laboratory Investigation:** Renal affection (Glomerular and tubular) will be monitored by the following:
- **Base Line (At Day 0):** Laboratory Investigations Including:
- Complete blood count and C-reactive protein, serum sodium, potassium, calcium phosphorus level and Kidney function test (Blood urea nitrogen and serum creatinine). Also, blood cultures and sensitivity test, urine analysis and arterial blood gases were done.
- **at Day 4 and on Discharge:** Laboratory investigations including:
- Serum cystatin C, a biomarker alternative to creatinine and creatinine clearance to screen for and monitor kidney dysfunction as cystatin C correspond to a decreased GFR.
- Serum and urinary Beta-2 microglobulin, for evaluation of renal tubular disease and to distinguish between disorders that affect the glomeruli and the renal tubules. All the chemical assays were done on Synchron CX5 automated chemistry analyzer (Beckman Diagnostic GmbH, Germany)
- **Imaging:** Imaging including cranial and abdominal ultrasonography for assessment of the kidney and urinary bladder was done by Adara-Sonoline equipped with concave linear transducer 5 MHz (Siemens Medical Systems, USA)
- **Radiological**
- Plain X ray for chest and abdomen.
- CT scan of the abdomen for liver, kidney and abdominal masses.
- Echocardiography in cases with suspected congenital heart disease by Sonoheart Elite (Sonosite, USA).

Statistical Methods: Statistical package for social science (SPSS) program version 10 was used for analysis of data. Parametric data was expressed as mean $\pm$SD and non-parametric data was expressed as number and percentage of the total.

Student's test for quantitative independent variables was done for analysis of difference between two groups. Chi-square test of significance was used in order to compare proportion between two categorical variables.

In all tests, p-value <0.05 is considered significant, p-value<0.01 is considered highly significant.

RESULTS

During the period of the study, the total number of admitted cases was 1143 neonates, signs or laboratory findings suggestive of kidney involvement was present in 80 (6.8%) neonates.

Figure (1): Shows the renal manifestations on general examination of the studied neonates. The most common renal manifestation was oedema in 34 (42.2%) patients. Bilateral renal enlargement was left in 14 (17.51) neonates bilateral renal parenchymal disease in one case, bilateral hydronephrosis in another case and bilateral cystic kidneys in 9 cases.

Causes of acute kidney injury in the studied neonates were demonstrated in (Table 1).

The studied neonates with and without AKI were compared for various risk factors (Table 2). The difference between the two groups was significant with respect to frequency of low birth weight, sepsis, associated DIC and shock (P<0.001).

Initial biochemistry profile of the studied groups revealed that the mean values of the blood urea nitrogen, creatinine, serum K and Ca were significantly higher among the neonates of AKI group in comparison to non AKI group (P<0.05) (Tables 3).

Although the last biochemistry profile was within normal still there was significant difference between AKI group in comparison to non AKI group (Table 4).

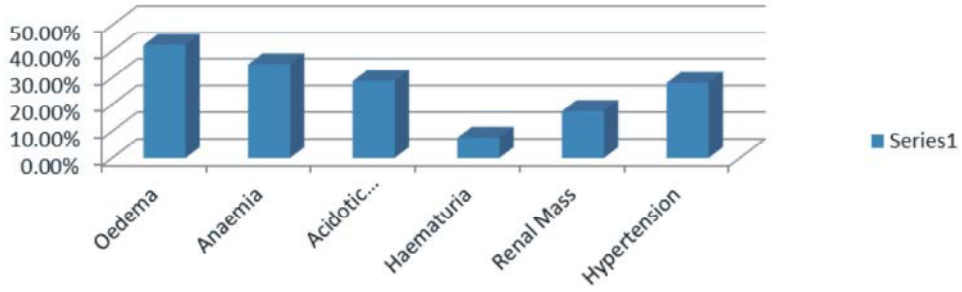

Fig. 1: Renal manifestations on general examination of the studied neonates:

Table 1: Causes of Acute Kidney Injury in the studied neonates:

Items	neonates	
Sepsis	27	(72.5%)
Bilateral renal hypoplasia/dysplasia	1	(1.2%)
Perinatal asphyxia	6	(7.5%)
Bilateral renal vein thrombosis	2	(2.5%)
Severe heart failure	2	(2.5%)
Unknown	1	(1.2%)

Table 2: Comparison of various risk Renal manifestations in AKI group and non-AKI group in the Studied neonates:

Items	AKI group (37)	Non-AKI group (43)	P-value
Mean gest. Age (wks)	35.5±2.4	36.6±2.5	0.41
Term = 37 wk	54%	57%	0.79
Preterm < 37 wk	36%	33%	0.2
Mean weight (kgs)	2.5±0.77	2.6±0.55	0.4
Wt< 2500 g	22%	14%	0.004*
Mean age at presentation (days)	2.62±2.46	3.48±3.9	0.6
Sepsis	64%	39%	0.003*
Culture positive sepsis	17%	22%	0.3
Co morbid conditions	44%	30%	0.07
DIC	65.1%	20%	0.001*
Shock	71%	27%	0.001*
Mortality	70%	25%	0.001*

*P- value is significant if <0.05

Table 3:Comparison of the last Biochemistry Profile in the studied groups:

	AKI group	Non-AKI group	
Items	Mean± SD	Mean± SD	P-value
BUN (mg/dl)	40.8±11.4	24.5±11	0.00*
Creatinine (mg/dl)	1.3±0.3	0.7±0.3	0.00*
Na (Mmol/L)	146.4±3.8	142.9±5.6	0.3
K (Mmol/L)	5.6±1.1	4.4±1.2	0.02*
Ca (mg/dl)	7.7±1	7.9±0.8	0.07
Ph (mg/dl)	4.2±1.2	4.09±0.6	0.10

*P- value is significant if <0.05

BUN= Blood urea nitrogen, Na= Sodium, K= Potassium, Ca= Calcium, Ph= Phosphate.

Table 4: Comparison of the initial Biochemistry Profile in the studied groups:

	AKI group	Non-AKI group	
Items	Mean± SD	Mean± SD	P-value
BUN (mg/dl)	21±7.1	18±6.5	0.00*
Creatinine (mg/dl)	0.6±0.28	0.5±0.2	0.00*
Na (Mmol/L)	146±3.8	142.9±5.6	0.36
K (Mmol/L)	4.6 ±0.1	4.4±1.1	0.03*
Ca (mg/dl)	7.7± 0.17	7.9±0.8	0.05*
PI (mg/dl)	4.2±1.1	4.0±0.61	0.10

*P- value is significant if <0.05

BUN= Blood urea nitrogen, Na= Sodium, K= Potassium, Ca= Calcium, PI= Phosphate.

Table 5: Serum Cystatin C and B2 microglobulin in the studied groups:

	AKI group	Non-AKI group	
Items	Mean ± (SD)	Mean (SD)	P-value
Cystatin C (mg/L)			
On admission	1.9 ± 0.31	1.3 ± 0.96	0.06
On day 4	2.9 ± 1.23	2.1 ± 0.82	0.02*
On discharge	3.2 ± 1.94	1.7 ± 0.61	0.00*
B2 microglobulin(μg/ml)			
On admission	0.02 ± 0.11	0.1 ± 0.11	0.07
On day 4	0.41 ± 0.16	0.3 ± 0.02	0.021*
On discharge	0.67 ± 0.22	0.29 ± 0.01	0.001*

*P- value is significant if <(0.05):

Table 6: Levels of Creatinine and Cystatin-C in relation to admission days:

Items	Creatinine(mg/dl)(Mean±SD)	Cystatin-C(mg/L)(Mean±SD)	P-value
On admission (day 0)	`0.6 ±0.28	1.9 ± 0.31	0.06
On (day 4)	1.1± 0.3	2.9±1.23	0.02*
On discharge	2.5 ± 0.7	3.2± 1.94	0.05

*P- value is significant if <0.05

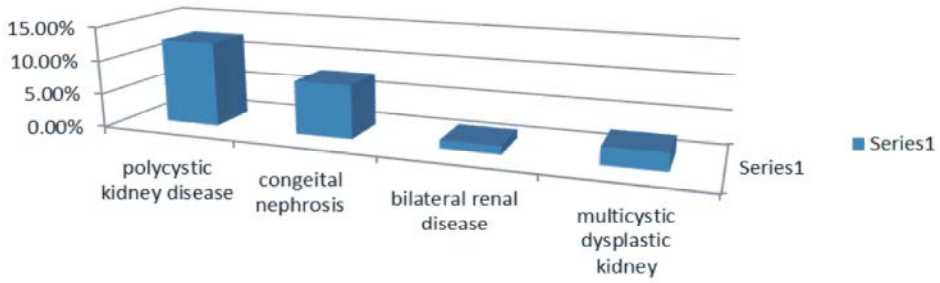

Fig. 2: Diagnosis of the Cases Referred to the Nephrology Clinic

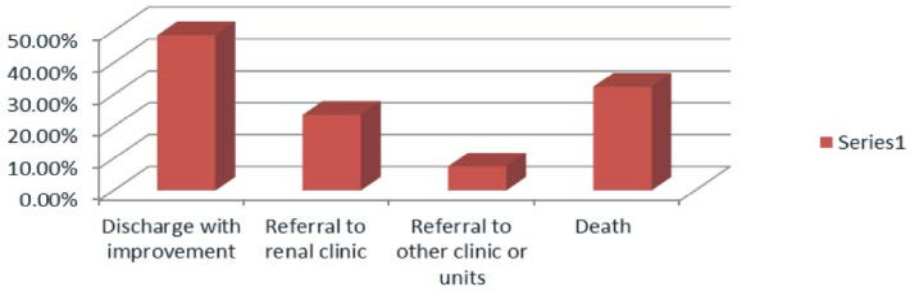

Fig. 3: Distribution of the Studied Neonates According to their Outcome

Table (5): Shows serum cystatin C and B2 microglobulin in the studied groups. The initial serum cystatin C and B2 microglobulin revealed no significant difference while at day 4 and on discharge there was significant difference between AKI in comparison with Non AKI group. ($P<0.05$).

Table (6): Demonstrates the level of creatinine and cystatine C in relation to admission days. The initial serum cystatin C and serum creatinine of the studied groups revealed that difference in the mean values was not significant (0.6 ± 0.28/ 1.9 ± 0.31, $P>0.05$) but the difference at day 4 was significantly higher among the neonates of AKI group as there is increase of serum cystatin C before the increase in serum creatinine (1.1 ± 0.3/ 2.9 ± 1.23, $P<0.05$). Meanwhile on discharge there was no difference.

Distributions of the studied neonates according to their outcome and diagnosis of the cases referred to the nephrology clinic were shown in Figure (2, 3).

DISCUSSION

This study was carried out through 12 months to highlight the occurrence of renal problems among neonates admitted to the neonatal intensive care units of the Children's Hospital, Cairo University.

Renal problems were either present initially in these neonates or developed later during the period of their hospital stay, AKI was the most common form of kidney affection and constituted 39 cases.

At the onset of AKI, the mean age of our studied cases was 6.7±0.5 days which is considerably higher than that reported by Andreoli [10] where early AKI occurrence (Aged; 0-5 days) was evident in 33 (77%) of their babies. This late onset AKI among our cases may be entirely related to the underlying etiology which was sepsis in 72.5%.

As sepsis was the 1st cause of AKI, Infection control measures - pre, intra- and postnatal are of utmost importance to overcome this high rate of neonatal sepsis with its high incidence of morbidity and mortality. (e.g.: proper antenatal care, strict antiseptic measures during handling of the babies in their early life, early detection of signs of neonatal sepsis with early and strong medical treatment [11, 12].

In our study, blood culture proven sepsis was the most common cause of AKI among the studied neonates, constituted 72.5% (27out of 37) of the cases. Out of them, gram negative organisms were isolated in 78.6% of cases, Klebsiella pneumoniae was the most common agent isolated (15%).

The incidence of neonatal sepsis in developed countries is 1-4/1,000 live births. Early onset disease can manifest as asymptomatic bacteremia, generalized sepsis, pneumonia and /or meningitis [7].

Several studies have evaluate relationships between infection and AKI, In the studies conducted by Badrawi *et al*. [13] Seoudi *et al*.[14] in NICU Kasr El Ainy hospital, Klebsiella pneumonia was the most frequently isolated organism occurring in 47.3%, 21.1% of cases respectively. Regarding renal manifestation associated with our study group oedema occurred in (42.2%) cases (34 cases out of 80), respiratory distress (Mainly metabolic acidosis) occurred in (40%) cases, elevated blood pressure occurred in (28%) and renal mass in (17.5%) cases this agrees with study done by Wilson *et al*. [15] Where oedema occurred in 39% of cases (23 cases out of 60), acidotic breathing occurred in 31% of cases (19 cases out of 60) and elevated blood pressure occurred in 28% (17 cases out of 60).

Regarding renal investigations we divide patients into two groups AKI group and Non-AKI group.

The initial biochemistry profile of the studied groups revealed a highly significant difference in the two groups regarding the mean values of the blood urea nitrogen, creatinine, K and Ca ($p<0.05$), as BUN and creatinine show the highest level in AKI group, this is due to renal function impairment [16].

Unexpectedly Na and Ph was not significantly higher in AKI group versus Non-AKI in spite of the decreased GFR in the former group, This can be explained by hyponatremic dehydration or fluid overload with dilutional hyponatremia which is much more common in AKI [17]. Also, Beth and Ellis [16] reported that tubular injury occurs early in the immature kidneys of the neonate causing loss of phosphate in urine.

Recent advances in the field of early AKI biomarkers have provided great optimism. Novel serum biomarkers may change our approach to this condition if they can indicate AKI hours after an insult; in comparison with the days it may take serum creatinine to rise substantially [18]. Biomarkers are currently being explored to differentiate between different causes of established AKI, to detect AKI early and to prognosticate outcomes. Currently, the most promising early non-invasive biomarkers of AKI are serum and urinary neutrophil gelatinase-associated lipocalin (NGAL) [19], urinary interleukin-18 (IL-18) [20], kidney injury molecule-1 (KIM-1) [21,22], serum cystatin C and B2 microglobulin [23]. Normal values in children are available [24].

Our results show the levels of serum Cystatin-C and B2microglobulin at different stages (At Day 0, Day 4 and on discharge). The difference was not significant ($P>0.05$) at initial stage between the two group which agree with study of Rosenthal *et al*. [25]. But the difference in day 4 and on discharge is significantly higher among the neonates of AKI group than the Non-AKI group ($p<0.05$). Lingos *et al*. [22] showed that there is a university proportionately when decreased GFR cause increase in Cystatin-C which was the same in our study.

It is to be noted that a significant difference ($p<0.05$) between the mean Cystatin-C and mean creatinine level at day 4 and not at day 0 and on discharge. As levels before day 4 is mostly maternal in origin, These findings suggest that Cystatin-C is a more sensitive marker in early detection of AKI preceding creatinine increase by few days which agree with study of Coca *et al*. [6] and Herget-Rosenthal *et al*. [25] as a 50% increase in serum Cystatin-C predict AKI 1-2 days prior to an elevation of serum creatinine.

Also Risch and Huber [26] found in their study that cystatin C may be a more accurate serum marker than creatinine in individuals with impaired renal function. Bdkenkamp *et al*. [27] reported in their study that Fetal serum concentrations of cystatin C appear to be useful predictors of postnatal renal function suggesting that this may become a more universal marker of glomerular function.

Cystatin C is a 13.6 kDa protease inhibitor constitutively synthesized by all nucleated cells that is freely filtered through the glomerulus and essentially completely Reabsorbed and catabolized by the tubular cells its measurement can now be performed by readily available immunoassay [23].

CONCLUSIONS

Although renal insult in babies admitted to NICU had a low prevalence (6.8%), yet with this group it contributed to the mortality of 30% of these cases.

AKI was the most common form of kidney affection and constituted (47.5%) of cases. Sepsis whether community acquired or hospital acquired was the major contributing factor for renal insult among our neonates. Sepsis, represented 72.5% of the affected neonates.

Serum Cystatine-C and B2Microglobulin may be considered as a sensitive predictive parameters for reduced GFR. It is of value for the laboratory diagnosis of AKI.

We Recommended: Early biomarkers of AKI as Cystatin-C and B2microglobulin need to be explored in critically neonates. Infants with AKI need to be followed for squeals after AKI.

Large prospective studies are needed to test definitions and better understand risk factors, incidence, independent outcomes and mechanisms that lead to poor short-and long-term outcomes of neonatal renal disorders.

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