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Premature twins with acute renal injury – it is not always what it seems to be: case report

Ivona Butorac Ahel[1], Ana Milardović[1], Kristina Lah Tomulić[1], Arijan Verbić[1], Sanja Flajšman Raspor[1], Đurđica Košuljandić[1], Ivana Štrk Romić[2]

Acute kidney injury (AKI) is common in critically ill premature infants. They are more susceptible to renal injury than older infants and children because of the functional and developmental immaturity of neonatal kidney. There is no unified definition for neonatal AKI. AKI in neonates is often multifactorial and may result from prenatal, perinatal, or postnatal insults as well. Serum creatinine (SCr) concentration at birth is similar to the mother's value. We present a case of prematurely born twins who were admitted to the paediatric intensive care unit because of AKI. Laboratory examination showed equally elevated levels of blood urea nitrogen (BUN) and SCr and metabolic alkalosis in both twins. High values of BUN and SCr were the result of the mother's unrecognized renal disease. On the seventh postnatal day, SCr and BUN in twins were within the normal ranges. In all cases with high SCr levels in neonates in the first 72 hours after birth, it is mandatory to check the mother's renal function.

Key words: acute kidney injury; infant; premature; uraemia

INTRODUCTION

Acute kidney injury (AKI) is an abrupt reduction in kidney function measured by a rapid decline in glomerular filtration rate (GFR) and in rise of serum creatinine (SCr) and blood urea nitrogen (BUN) (1). There is no unified definition for diagnosing neonatal AKI. Before 2008, a frequently used definition was SCr level more than 133 µmol/L (1.5 mg/dL) or rising SCr by at least 17 to 27 µmol/L (0.2 to 0.3 mg/dL) *per* day (2). In 2004, the Acute Dialysis Quality Initiative group proposed the RIFLE (Risk, Injury, Failure, Loss, End-Stage) criteria for AKI diagnosis (3). These criteria have been modified to paediatric RIFLE (pRIFLE) (4) and the AKI network (AKIN) criteria. In 2013, the Kidney Disease: Improving Global Outcomes (KDIGO) proposed a definition of neonatal AKI, in which it was classified as mild (acute increase of SCr above baseline to 150%-200%), moderate (acute increase of SCr above baseline to 200%-300%) and severe (acute increase of SCr above baseline >300% or dialysis) (5). These definitions are applicable to infants in the first 120 days of life. The group of neonatologists and paediatric nephrologists at the National Institute of Health (NIH), the Neonatal AKI Workshop recommended the use of this definition (1). By applying KDIGO definition, approximately 18% of low birth weight (LBW) infants developed some degree of AKI during their hospital stay, which was independently associated with an increased mortality of 42% (6, 7). The mortality in infants with AKI was significantly higher than in those without AKI (42% *vs*. 5%) (8). Early identification of high-risk newborns and appropriate treatment of neonatal AKI are among clinical imperatives in neonatology.

We present a case of premature twins born with high values of SCr resulting from unrecognized and untreated mother's renal failure.

[1] Clinical Department of Paediatrics, Rijeka University Hospital Centre, Rijeka, Croatia
[2] Department of Paediatrics, Pula Regional Hospital, Pula, Croatia

Correspondence to:
Ivona Butorac Ahel, MD, MS, Clinical Department of Paediatrics, Rijeka University Hospital Centre, Istarska 43, HR-51000 Rijeka, Croatia,
E-mail: ivonabuah@gmail.com

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TABLE 1. Results of laboratory investigations of twins and their mother

Day of hospitalization	First			Third		Before dicharge		
Laboratory results	First twin	Second twin	Mother	First twin	Second twin	First twin	Second twin	Mother
Erythrocytes (x10^{12}/l)	4.30	4.44	4.61	3.25	4.02	4.66	3.85	/
Hemoglobin (g/l)	164	179	131	164	162	154	117	/
Hematocrit (l/l)	0.463	0.509	0.385	0.463	0.455	0.436	0.344	/
Leukocytes (x10^{9}/l)	5.2	11.4	10.66	5.2	11.7	10.1	7.6	/
Platelets (x10^{9}/l)	232	285	185	212	292	528	292	/
Urea (mmol/l)	21.1	20.9	19.9	9.6	10.0	6.2	3.6	6.6
Creatinine (µmol/l)	288	291	282	159	136	55	55	171
Sodium (mmol/l)	127	126	129	132	133	140	139	133
Potassium (mmol/l)	2.9	3.1	2.4	2.8	4.5	4.9	5.7	3.1
Chloride (mmol/l)	69	70	72	90	94	110	111	82
Calcium (mmol/l)	2.11	2.24	2.29	1.26	1.16	2.49	2.4	2.2
Glucose (mmol/l)	4.0	10.8	6.6	6.9	10.6	5.5	5.4	6.6
pH	7.6	7.48	/	7.48	7.48	7.35	7.37	/
HCO3 (mmol/l)	50.8	34.9	/	30.7	28.2	21.6	19,7	/
Base excess (mmol/l)	29	9.8	/	6.5	4.4	-4	-4.7	/

CASE REPORT

Two prematurely born twins were transferred three and a half hours after delivery from a regional hospital to the Paediatric Intensive Care Unit, Rijeka University Hospital Centre. It was a twin dichorionic and diamniotic pregnancy. Since the pregnancy was uncontrolled, there were no data on the placental function and growth, but after delivery there were no signs of placental malfunctioning. The estimated gestational age of twin girls was about 32 weeks, their birth weights were below the third percentile for gestational age (1080 g and 1100 g, respectively). APGAR scores were 6/6 and 5/5, respectively. The newborns were intubated, intratracheal surfactant was administered and they were transferred to our care. Upon arrival, the twins were slightly hypothermic (body temperature was 35 °C and 36 °C, respectively) with bluish flanks. They were breathing spontaneously with regular frequency (both about 40/min), SpO_2 in room air was 88% and 89%, with regular pulse (120/min and 134/min) and blood pressure (49/30 mm Hg and 70/30 mm Hg). Chest x-ray indicated mutual perihilar shading as part of the respiratory distress syndrome (RDS). Nasal Continuous Positive Airway Pressure (nCPAP) was initiated. Laboratory tests of both twins are shown in Table 1. They revealed profound azotaemia of equal values of BUN and SCr, as well as electrolyte imbalance, e.g., hyponatremia, hypochloraemia, borderline hypokalaemia, and marginal hypocalcaemia. Both twins had metabolic alkalosis. Very soon after admission, both twins had meconium. The urine output was normal (about 2.5 mL/kg/h). Nephrology examinations included kidney ultrasound scans and urine samples. The results matched the normal values in premature infants of their gestational age. To determine the aetiology of their condition, we suspected that the mother had been suffering from renal injury, which led to transplacental transfer of toxins. Maternal SCr value was determined and it was found to be the same as in the newborns (282 µmol/L). In the following days, continuous decline in BUN and SCr values was present, as well as balancing the value of acid-base status and electrolytes. On the seventh postnatal day, these values were normalized and the infants' overall condition was stable. They were discharged after 60 days, their weight was 2420 g and 2480 g, respectively.

Later, we found out that the twins' mother started vomiting and had abdominal pain without diarrhoea three days before her preterm delivery. She had no history of renal disease. SCr and BUN were controlled after 24 hours and had a decreasing tendency (BUN 15.6 mmol/L, SCr 171 µmol/L). The cause of her illness remained unidentified because she left the hospital on her own demand, without finishing diagnostic tests.

DISCUSSION

In premature infants, the kidney size and nephron number are reduced due to disruption of organogenesis and arrest in branching organs at a crucial developmental period. Nephrogenesis in the human foetus is completed by the 35th week of gestation with more than 60% of nephrons being formed in the last trimester of pregnancy (6, 9, 10). Preterm birth forces developmental adaptation to an extrauterine environment with immediate, short- and long-term implications. Molecular pathologic mechanisms that play a role in reducing nephron endowment include inflammato-

ry cytokines, hyperoxia, and antiangiogenic factors. Additional kidney injury from hypoperfusion and nephrotoxicity results in structural and functional changes over time, which often are unnoticed. Nephropathy of prematurity and AKI confound glomerular and tubular maturation of preterm kidneys (7). Reduced nephron numbers and limited function make the impact and consequences of postnatal renal insults in preterm infants greater (7).

Several factors have been identified as risk factors for development of neonatal AKI including LBW (<1500 g), low APGAR score, intubation at birth, RDS, need for mechanical ventilation, vasopressor support for hypotension, hemodynamically significant PDA, male gender, sepsis, phototherapy, and maternal and neonatal drug administration (6, 11, 12). The causes of AKI in newborns are multiple and are categorized as prerenal, renal and postrenal. In neonates, prerenal azotaemia is the most common type of AKI and may account for up to 85% of all cases (13). It is due to decreased renal perfusion, which, if treated inappropriately, may lead to acute tubular necrosis. Renal failure is caused by renal vascular thrombosis or congenital/genetic renal disorders. Obstructive lesions of urinary tract cause postrenal failure, which can be simply identified by performing renal ultrasound scan. Assessment of renal function in premature infants is difficult and limited. AKI is suspected in newborns with anuria, oliguria, oedema, elevated or rising SCr, and electrolyte imbalances. Clinical signs suggestive of AKI may be late or nonspecific. Also, since up to 60% of neonatal AKI is non-oliguric, oliguria and anuria are late signs and have limited sensitivity (14). SCr is still the most commonly used marker of renal function and the gold standard to diagnose AKI. However, SCr is not an ideal marker of AKI in neonates for several reasons. During pregnancy and in the first 72 hours of life, foetal and neonatal SCr concentration reflects the mother's and not the newborn's renal function. Besides, the concentrations of SCr may not change until 25%-50% of the kidney function has already been lost, and it may take days before a significant rise in SCr is noticed. Also, the value of SCr is influenced by age, muscle mass, and maturity (7). Since there are numerous difficulties in defining neonatal AKI, effort has been made to identify novel biomarkers to predict AKI before SCr increase or urine output reduction (14). There are several possible AKI biomarkers including serum cystatin C, urinary interleukin-18 (IL-18), serum and urinary neutrophil gelatinase-associated lipocalin (NGAL), kidney molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP), angiotensinogen, tissue inhibitor of metalloproteinase-2, IGF-binding protein 7, osteopontin (OPN) and beta-2 microglobulin (14). Before their use in routine clinical practice, further long-term studies are needed.

Renal failure during pregnancy affects both the mother and the foetus, and may be related to pre-existing disease or develop secondary to diseases of pregnancy. Preeclampsia is the most common cause of AKI during pregnancy. Other possible causes include hypovolemia, sepsis, shock, thrombotic microangiopathies, and renal obstruction (15). Pregnancy-related AKI and chronic kidney disease are a significant and independent risk factor for adverse maternal and fetal outcomes including miscarriage, preterm delivery, preeclampsia, and maternal and fetal death (16, 17). Even pregnant women with mild decrease in GFR are at an increased risk of adverse events compared to those without kidney disease (17).

Our infants had several risk factors for developing AKI, i.e. very low birth weight, intubation at birth, and RDS. Renal ultrasound scans in both babies showed the presence of two kidneys normal in size, shape and echogenicity. Urinary tract obstruction was excluded. Because premature twins had almost identical high SCr value, the value of maternal SCr was determined and was the same as those in the twins. The coexistence of metabolic alkalosis and renal failure is unusual, but may occur. There are two possible mechanisms of development of metabolic alkalosis. Vomiting or diuretic therapy may result in volume depletion, loss of Na^+, Cl^-, H^+ and increased HCO_3^- reabsorption in the tubules. Treatment with exogenous bicarbonate can also result in metabolic alkalosis (18). We assume that mother's vomiting led to volume depletion, electrolyte imbalance and metabolic alkalosis in her and the babies.

A limitation of this case report is the fact that the aetiology of the mother's renal injury remained unclear. We can speculate that she had impaired renal function, which was aggravated by vomiting and dehydration, but definitive diagnosis remained unclear. Nevertheless, we present a rare cause of high levels SCr in premature babies. It is important to recognize these benign, self-resolving conditions in differential diagnosis and to avoid unnecessary, expensive and often painful medical interventions in newborns. When high SCr values are detected in neonates during the first three days of their lives, clinicians should exclude maternal kidney disease as a possible cause.

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SAŽETAK

Nedonešeni blizanci s akutnim oštećenjem bubrega – nije uvijek kako se čini: prikaz slučaja

Ivona Butorac Ahel, Ana Milardović, Kristina Lah Tomulić, Arijan Verbić, Sanja Flajšman Raspor, Đurđica Košuljandić, Ivana Štrk Romić

Akutna bubrežna ozljeda je česta u prijevremeno rođene novorođenčadi. Zbog funkcijske i razvojne nezrelosti bubrega oni su osjetljiviji na bubrežnu ozljedu u odnosu na stariju dojenčad i djecu. Ne postoji jedinstvena definicija za akutnu bubrežnu ozljedu u novorođenčadi. Etiologija bubrežne ozljede je često multifaktorska i može nastati kao posljedica prenatalnih, perinatalnih i postnatalnih zbivanja. Koncentracija serumskog kreatinina novorođenčeta u trenutku porođaja podjednaka je majčinoj. Prikazujemo slučaj prijevremeno rođenih blizanki koje su primljene u Jedinicu intenzivnog liječenja zbog akutne bubrežne ozljede. Rezultati laboratorijskih analiza su pokazali podjednako povišene vrijednosti ureje i serumskog kreatinina obiju blizanki, praćene metaboličkom alkalozom. Povišene vrijednosti ureje i serumskog kreatinina bile su posljedica majčine neprepoznate bubrežne bolesti. Sedmog postnatalnog dana vrijednosti kreatinina i ureje su se normalizirale. U svim slučajevima povišenih vrijednosti serumskog kreatinina u prva 72 sata života nužno je evaluirati majčinu bubrežnu funkciju.

Ključne riječi: akutna bubrežna ozljeda, prijevremeno rođena novorođenčad, uremija