

Acute kidney injury in an extremely low birth weight infant with nephrolithiasis: a case report

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Acute kidney injury is associated with mortality of very low birth weight infants and reduces their survival regardless of other factors. The kidneys in the extremely preterm infants are very immature and susceptible to environmental factors. Clinical conditions and medications are risk factors for acute kidney injury in these patients. Nephrolithiasis in preterm infants is an extremely rare phenomenon that usually manifests as a complication of nephrocalcinosis.

This is a case report that describes several episodes of acute kidney injury in the first two months of age in an extremely low birth weight infant with kidney stones in the background. The main causes that led to acute kidney injury in this patient were persistent ductus arteriosus, sepsis and captopril. At one month of age, ultrasound detected calcinates in the right kidney. Within two weeks a large number of linear stones formed across the collecting duct system. Small calcinates still remained in the right kidney when the girl was half a year of the corrected age.

The evaluation of a neonate who develops acute kidney injury requires a systematic approach. Early identification of the emerging risk factors and prevention of nephrolithiasis along with effective treatment can reduce the risk of developing acute kidney injury in very low birth weight infants.

Keywords: acute kidney injury; nephrolithiasis; preterm infant

INTRODUCTION

Adaptation of extremely-low-birth-weight (ELBW) infants requires long-term treatment of diseases caused by prematurity as well as of congenital and acquired diseases. The kidneys in ELBW infants are very immature and susceptible to environmen-

tal factors. This may affect the kidney function. Acute kidney injury (AKI) occurs in 1.5–10.8% of the infants treated in the intensive care unit (1, 2). In the group of very low birth weight (VLBW) infants, AKI account for 18% (3). This percentage is thought to be higher because preterm infants may have nonoliguric kidney injury (1). In most cases, up to 96% of prerenal form of acute kidney injury occurs in very- low-birth-weight infants as a result of kidney hypoperfusion and ischemia (1, 4). Studies

show that AKI is associated with mortality of VLBW infants and reduces their survival regardless of other factors (3, 5).

Nephrolithiasis in preterm infants is an extremely rare phenomenon. In most cases it is manifested as a complication of nephrocalcinosis, which occurs in 6–41% of infants weighing up to 1500 grams (6–10). Kidney stones in preterm infants cause recurrent urinary tract infections, microhaematuria, (6) and sometimes urinary tract obstruction requiring surgical intervention (6, 11). It can progress to chronic kidney disease (7).

We present a case of an extremely-low-birth-weight female, born at 23 weeks. She had several episodes of acute kidney injury and kidney stones.

CASE REPORT

A female neonate A. was born at 23 weeks of gestation, weighing 590 grams, to a 28-year-old grav-

id 2, para 2 mother. The infant's Apgar scores were 5/7 at 1 and 5 min. The infant's condition at birth was complicated. Mechanical ventilation was initiated along with antibiotic therapy with penicillin and gentamicin, and cefotaxime was initiated later. Per protocol, parenteral nutrition with amino acids and intralipids was initiated after birth. Vitamin D was started from day 12 of life with 400 IU per day. Brain and kidney ultrasound images were within the normal range in the first week of life.

On day 3 of life, patent ductus arteriosus (PDA) was diagnosed by echocardiogram. The first course of ibuprofen was started for three days. The ductus arteriosus remained open after the second course of ibuprofen, which was completed on day 16 of life. Reverse diastolic blood tide was visible in the brain. On day 19 of life, hyperkalemia was observed in the capillary blood for two days (6→6.8→9→5.8 mmol/L, normal value is 3.4–5.6 mmol/L) (Fig. 1). Diuresis did not change on

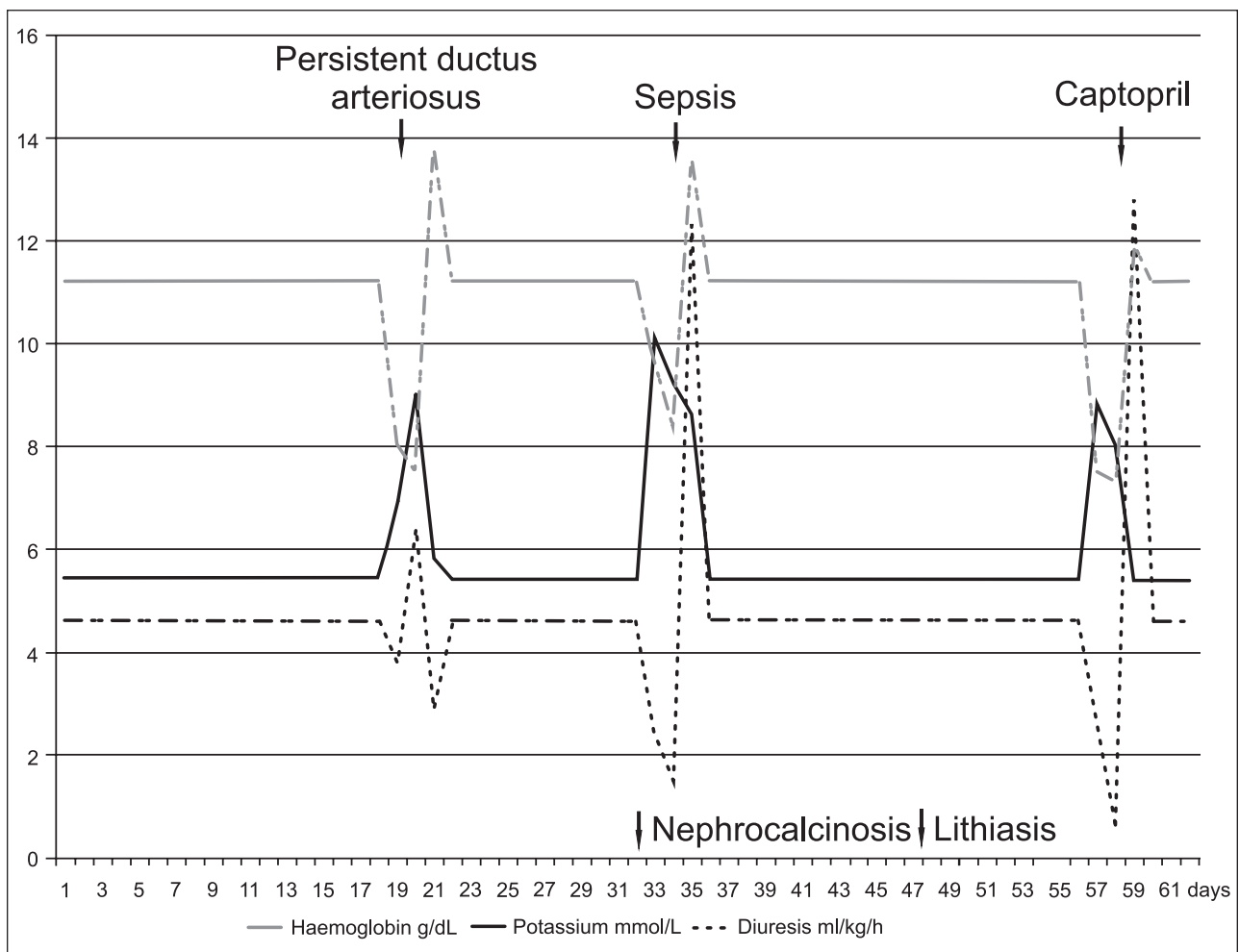


Fig. 1. Episodes of acute kidney injury with risk factors

these days and was at a range of 3.8–6.4 ml/kg/hour. Therefore kidney ultrasound was not done. PDA ligation carried out on day 23 of life went smoothly. Before the surgery a red blood cell transfusion was done for a blood haemoglobin (Hb) level 7.5 g/dL.

After the surgery, the infant was in a stable condition. The high-frequency oscillation ventilation was continued. Due to unsuccessful attempts to extubate on day 28 of life, a three-day course of dexamethasone therapy was started. The condition deteriorated on day 33 of her life as a result of an unspecified sepsis. She developed fever. Inflammatory markers in the blood increased. The urine output was lower than average (4.6→1.5 ml/kg/h) and peripheral oedema spread. Severe hyperkalemia (up to 10.1 mmol/L) manifested in the blood (Fig. 1). Ventricular extrasystoles were being observed in electrocardiogram, and infusion therapy with glucose and calcium gluconate was started. Antibacterial therapy with amikacin was effective. Subsequently, there was a dramatic increase in diuresis (to 12.3 ml/kg/hour) for one day. To maintain fluid and electrolyte stability, infusion therapy with electrolytes was continued along with the parenteral nutrition. However, there were no changes in the general urine test. The creatinine level in the blood was not tested. Blood transfusion was performed (when Hb was 8.4 g/dL) without complications. Ultrasound detected large linear calculi in the right kidney along the walls of the collecting duct system. Within two weeks a large number of linear stones formed across the collecting duct system. No changes were detected in the left kidney.

For two weeks the girl's condition was stable. She was fully enterally fed, continuous positive airway pressure was used. Later, on day 52 of life, a urinary tract infection complicated the condition of the infant. Biochemical markers of kidney function (creatinine and blood level of urea) were within normal limits. Cefuroxime was added. On the second day of illness her condition improved and she had no fever. On the third day of illness, secondary arterial hypertension was treated with captopril. The first clinical symptom of kidney injury appeared after the second dose of captopril. Oliguria (to 0.6 ml/kg/hour) and oedema rapidly progressed (Fig. 1). Kidney injury was obvious as a result of the following features: hyperkalemia (to 8.8 mmol/L), el-

evated creatinine (173 µmol/L, the normal value is 15–37 µmol/L) and urea (8.98 mmol/L, the normal value is 1.7–8.3 mmol/L) levels in the blood. After the fourth dose, treatment with captopril was discontinued. Glucose infusion with sodium bicarbonate and calcium gluconate was applied. Diuresis was stimulated with furosemide just once because of hyperkalemia in the blood and oliguria despite the stones in kidney. Polyuria developed. When the level of potassium in the blood decreased, red cell mass was transfused for the third time (at Hb 7.3 g/dL). The condition improved during the day. Blood creatinine level decreased after 24 hours to 71 µmol/L, and returned to its baseline values (29 µmol/L) after two days. Ultrasonography of kidney stones was with no changes. Elevated level of calcium was detected in urine (calcium/creatinine 1.3).

The patient did not have recurrent kidney failure any longer. She was gaining weight well; the neurological status was in accordance to the corrected age. The kidney stones were treated with potassium citrate prescribed by a pediatric nephrologist. Before she was discharged from the hospital, smaller changes were observed in the right kidney in the repeated ultrasonography of the urinary tract: a large number of small calculi, which in some places merged into linear calculi, were observed (see Fig. 2). A geneticist suggested a workup for the congenital hyperoxaluria. The level of organic acids in the urine was within its normal values. Because of high amount of vitamin D (25-OH) in the blood and of the calculi in the kidney, vitamin D was not given for three weeks before discharge. There was no family history of kidney stones.

The girl was discharged from the hospital in a satisfactory state at 126 days of age (41 weeks of corrected age), weighing 3180 grams. The patient's follow up by a child nephrologist was recommended. Kidney function tests showed normal values. However, small calculi still remained in the right kidney and hypercalciuria was found in the urine when the girl was half a year of the corrected age.

DISCUSSION

To the best of our knowledge, this is the first case report which describes several episodes of acute



Fig. 2. Calcinates in the right kidney before discharge

kidney injury in an extremely-low-birth-weight infant with kidney stones formed. Clinical conditions and medications for our patient were known risk factors for acute kidney injury. Nephrocalcinosis and, later, numerous linear stones within the entire right collecting duct system could restrict the kidney function at a critical moment.

The first nonoliguric episode of acute kidney injury manifested itself when the infant in the case described was three weeks of age. Studies report more than 50% of AKI cases to be nonoliguric, which highlights the insensitivity of oliguria in predicting AKI in neonates (12). At that time, the infant's condition was deteriorating because of persistent ductus arteriosus. In up to 8.1% of cases, PDA can be the cause of acute kidney injury (2). Although the creatinine level in the blood was not tested at that time, significant hyperkalemia was observed. There are few important factors that should be considered. In the case of the clinically significant persistent ductus arteriosus, the blood flow decreases because of the reversing diastolic wave in the descending aorta and in kidney and mesenteric blood vessels (13, 14). The so-called

ductal steal phenomenon of the peripheral circulatory system during diastole could have had an effect on kidney blood flow (doppler ultrasonography was not performed to assess kidney blood flow in the case described above). The drug initially used to treat PDA was ibuprofen, which may induce preglomerular arteriole vasoconstriction on rare occasions. It reduces renal blood flow and the glomerular filtration rate in VLBW infants through the inhibition of prostaglandin synthesis (15, 16). The patient was also treated with aminoglycosides. These drugs are known to cause nephrotoxicity, which is characterized by a nonoliguric clinical picture (17).

Another episode of acute kidney injury was observed when the condition was worsening due to unspecified sepsis with expressed nephrocalcinosis in the background. Neonates who develop sepsis are thought to be predisposed to AKI secondary to the hypotension associated with systemic inflammation, but there also appears to be a direct impact on the kidneys (18). Various studies show that sepsis was a predisposing factor of acute kidney injury in the 63–77.5% of cases (1, 2).

Calcinates in the patient's right kidney were diagnosed using ultrasound. There is a clear correlation between prevalence of nephrocalcinosis (NC) and low gestational age. According to the research data, nephrocalcinosis develops as a result of imbalances between the factors that promote or inhibit formation of kidney stones. It is caused by intensive treatment as well as functional and morphological immaturity of the kidney (8, 11). High serum levels of vitamin D may play an important role in the pathogenesis of urolithiasis in infants with hypercalcemia (19). Mostly, nephrocalcinosis disappears by itself but in individual cases it manifests by the formation of stones that complicate the course of the disease and may have long-term consequences. A clinical case of one neonate, born at the 27th week of gestation, with the birth weight of 850 grams, was described (7). She was two months old when her diagnosis of nephrocalcinosis with multiple stones in both kidneys was made. The left kidney atrophied over time. At the age of seven, the patient was being treated for hypertension and chronic kidney disease. Calcinates were found in the right kidney and the left ureter of another girl (at 28-week gestational age, birth weight of 900 grams) after her kidney function was impaired on day 33 of age (20). Hydronephrosis in the left kidney developed with urinary tract obstruction, and subcapsular and perinephric urinoma was also observed. Percutaneous drainage was conducted successfully. At the age of eight months, the patient had a normal kidney function, hydronephrosis and kidney stones were not detected. In one retrospective study of VLBW infants of up to one year of age, nephrocalcinosis was diagnosed in 11 patients, one of whom had stones formed (6). The disease manifested with recurrent urinary tract infection and haematuria. In the case of our patient (who was the smallest among the reported cases), stones began to dissolve while the patient was still in hospital and at the sixth month of the corrected age only traces of them remained.

Biochemical indicators were within normal reference range, with kidney stones and urinary tract infection in the background when the angiotensin-converting enzyme (ACE) inhibitor captopril provoked another acute kidney injury. Lower levels of angiotensin II production are known to result in lower glomerular filtration rate via dilata-

tion of renal efferent arterioles (16). After the first dose, nephrotoxic effects of ACE inhibitors may provoke acute kidney injury, particularly in infants with congenital heart defects and those born prematurely (21–23). Insignares-Vizcaino et al. describe an infant of 29 weeks of gestational age who was given enalapril to treat the symptoms of congenital heart defects on day 6 of life (24). Diuresis was disturbed after the first dose already. Peritoneal dialysis was applied. The kidney function recovered on day 34 of life. The first clinical signs of kidney injury in our patient appeared after the second dose of captopril, which is more of a short-term inhibitor of ACE than enalapril. Hyperkalemia developed. After intensive treatment, kidney function went back to normal and the condition stabilised within three days. As has been described in the literature, early kidney dysfunction may reverse when the treatment is terminated but once anuria sets in, the prognosis is generally bad (16, 22). Subsequent kidney injury was not observed in our patient.

In all three episodes of acute kidney injury the transfusion of red blood cells was performed according to the anaemia protocol applied in the hospital. Kidney injury and hyperkalemia were apparent before the transfusion was performed. Therefore, it was not a complication of the transfusion, as has been described in the literature (25). Non-invasive near-infrared spectroscopy that monitors regional tissue oxygenation was used to detect that transfusions of the red blood cells improve kidney regional blood flow (26) which may affect the development of acute kidney injury in VLBW infants (1).

We suppose that the main causes that led to AKI in this extremely-low-birth-weight girl were persistent ductus arteriosus, sepsis, and captopril. Some other important factors, such as use of nephrotoxic drugs, steroids, and longer use of ventilator and parenteral nutrition are associated risk factors of AKI in ELBW infants, according to the literature data (27). These factors also predispose nephrocalcinosis and nephrolithiasis, along with immaturity of kidney in VLBW infants. Even if kidney ultrasound did not show us echoscopic changes in the collectoric duct system (stones did not dislodge) in our patient, we did not know about intratubular crystallization events that could lead to an obstructive uropathy on a microscopic

level in the acute phase of kidney injury in this particular child (28).

Special attention should be given to the kidney function because of the immaturity and vulnerability of extremely low birth weight infants.

CONCLUSIONS

Evaluation of a neonate who develops acute kidney injury requires a systematic approach that frequently involves evaluating prerenal, intrinsic, and postrenal causes. In the case of acute kidney injury of VLBW infants, both the treatment and the injury itself increase the risk of morbidity during first months of life. Therefore, early identification of the emerging risk factors and effective treatment can reduce the risk of developing acute kidney injury in very low birth weight infants. Prevention and diagnosis of nephrocalcinosis and kidney stones remain an important problem in neonatology.

DECLARATION OF INTERESTS

The authors declare that they have no conflict of interests.

INFORMED CONSENT

Written informed consent was obtained from the legal guardians of the patient for the purposes of publication of this case report and of any accompanying images.

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References

1. Youssef D, Abd-Elrahman H, Shehab MM, Abd-Elrheem M. Incidence of acute kidney injury in the neonatal intensive care unit. *Saudi J Kidney Dis Transpl.* 2015; 26(1): 67–72.
2. Momtaz HE, Sabzehei MK, Rasuli B, Torabian S. The main etiologies of acute kidney injury in the newborns hospitalized in the neonatal intensive care unit. *J Clin Neonatol.* 2014; 3: 99–102.
3. Koralkar R, Ambalavanan N, Levitan EB, McGwin G, Goldstein S, Askenazi D. Acute kidney injury reduces survival in very low birth weight infants. *Pediatr Res.* 2011; 69: 354–8.
4. Ottonello G, Dessì A, Neroni P, Trudu ME, Manus D, Fanos V. Acute kidney injury in neonatal age. *J Pediatr Neonat Individual Med.* 2014; 3(2): e030246. doi: 10.7363/030246.
5. Askenazi AJ, Griffin R, McGwin G, Carlo W, Ambalavanan N. Acute kidney injury is independently associated with mortality in very low birthweight infants: a matched case-control analysis. *Pediatr Nephrol.* 2009; 24: 991–7.
6. Chang H-Y, Hsu C-H, Tsai J-D, Li S-T, Hung H-Y, Kao H-A, Chang J-H, Chung H-Y, Wang H-K. Renal calcification in very low birth weight infants. *Pediatr Neonatol.* 2011; 52: 145–9.
7. Kim HS, Jeong K, Choi YY, Song ES. Risk factors and outcome of nephrocalcinosis in very low birth weight infants. *Korean J Perinatol.* 2015; 26(1): 35–45.
8. Schell-Feith EA, Kist-van Holthe JE, van der Heijden AJ, Conneman N, van Zwieten PH, Holscher HC, Zonderland HM, Brand R, van der Heijden BJ. Etiology of nephrocalcinosis in preterm neonates: association of nutritional intake and urinary parameters. *Kidney Int.* 2000; 58: 2102–10.
9. Narendra A, White MP, Rolton HA, Alloub ZI, Wilkinson G, McColl JH, Beattie J. Nephrocalcinosis in preterm babies. *Arch Dis Child Fetal Neonatal Ed.* 2001; 85: F207–13.
10. Porter E, McKie A, Beattie TJ, McColl JH, Aladangady N, Watt A, White MP. Neonatal nephrocalcinosis: long term follow up. *Arch Dis Child Fetal Neonatal Ed.* 2006; 91: F333–6.
11. Schell-Feith EA, Kist-van Holthe JE, van der Heijden AJ. Nephrocalcinosis in preterm neonates. *Pediatr Nephrol.* 2010; 25: 221–30.
12. Zübarioğlu AU, Bülbül A, Uslu HS. Neonatal acute kidney injury. *JAREM.* 2013; 3: 53–9.
13. Groves AM, Kuschel CA, Knight DB, Skinner JR. Does retrograde diastolic flow in the descending aorta signify impaired systemic perfusion in preterm infants? *Pediatr Res.* 2008; 63: 89–94.
14. Shimada S, Kasai T, Hoshi A, Murata A, Chida S. Cardiocirculatory effects of patent ductus arteriosus in extremely low-birth-weight infants with respiratory distress syndrome. *Pediatr Int.* 2003; 45: 255–62.
15. Vieux R, Desandes R, Boubred F, Semama D, Guillemin F, Buchweiller M-C, Fresson J, Hascoet J-M. Ibuprofen in very preterm infants impairs renal function for the first month of life. *Pediatr Nephrol.* 2010; 25: 267–74.

16. Zappitelli M, Selewski DT, Askenazi DJ. Nephrotoxic medication exposure and acute kidney injury in neonates. *Neoreviews*. 2012 Jul; 13(7): e421.
17. Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. *Kidney Int*. 2011; 79: 33–45.
18. Selewski DT, Charlton JR, Jetton JG, Guillet R, Mhanna MJ, Askenazi D, Kent AL. Neonatal Acute Kidney Injury. *Pediatrics*. 2015; 136: e463.
19. Fallahzadeh MH, Zare J, Al-Hashemi GH, Derakhshan A, Basiratnia M, Arasteh MM, Fallahzadeh MA, Fallahzadeh MK. Elevated serum levels of vitamin D in infants with urolithiasis. *Iran J Kidney Dis*. 2012; 6(3): 186–91.
20. Alpert SA, Noe HN. Furosemide nephrolithiasis causing ureteral obstruction and urinoma in a preterm neonate. *Urology*. 2004; 64(3): 589.
21. Lee GJ, Cohen R, Cleary JP. Angiotensin converting enzyme inhibitor (ACEI)-induced acute renal failure in premature newborns with congenital heart disease. *J Pediatr Pharmacol Ther*. 2010; 15: 290–6.
22. Dutta S, Narang A. Enalaprilinduced acute renal failure in a newborn infant. *Pediatr Nephrol*. 2003; 18(6): 570–2.
23. Lindle KA, Dinh K, Moffett BS, Kyle WB, Montgomery NM, Denfield SD, Knudson JD. Angiotensin-converting enzyme inhibitor nephrotoxicity in neonates with cardiac disease. *Pediatr Cardiol*. 2014; 5: 499–506.
24. Insignares-Vizcaíno ZM, Echeverri-Cardona M, Fernández-Laverde M. (Acute renal failure induced for enalapril). *Injuria renal aguda neonatal por enalapril*. *Rev CES Med*. 2013; 27(1): 83–91. Spanish.
25. Lee AC, Reduque LL, Luban NLC, Ness PM, Anton B, Heitmiller ES. Transfusion-associated hyperkalemic cardiac arrest in pediatric patients receiving massive transfusion. *Transfusion*. 2014; 54: 244–54.
26. Seidel D, Bläser A, Gebauer C, Pulzer F, Thome U, Knüpfer M. Changes in regional tissue oxygenation and saturation and desaturations after red blood cell transfusion in preterm infants. *J Perinatol*. 2013; 33: 282–7.
27. Arcinue R, Kantak A, Elkhwad M. Acute kidney injury in ELBW infants (<750 grams) and its associated risk factors. *J Neonatal Perinatal Med*. 2015; 8: 349–57.
28. Tang X, Lieske JC. Acute and chronic kidney injury in nephrolithiasis. *Curr Opin Nephrol Hypertens*. 2014; 23(4): 385–90.

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YPAČ MAŽO GIMIMO SVORIO NEIŠNEŠIOTO NAUJAGIMIO SU INKSTŲ AKMENLIGE ŪMUS INKSTŲ PAŽEIDIMAS: ATVEJO PRISTATYMAS

Santrauka

Įvadas. Labai anksti gimusių neišnešiotų naujagimių ūmus inkstų pažeidimai susiję su mirštamumu, jų išgyvenamumas mažėja nepaisant kitų aplinkybių. Gimusių ypač mažo svorio naujagimių inkstai yra labai nebrandūs ir jautrūs aplinkos poveikiui. Klinikinės būklės ir medikamentai yra šių pacientų ūmaus inkstų pažeidimo rizikos veiksniai. Naujagimių inkstų akmenligė – reta liga, dažniausiai pasireiškianti kaip neišnešiotų naujagimių nefrokalcinozės komplikacija.

Atvejo aprašymas. Aprašomas neišnešiotas naujagimė (23 savaičių gestacinio amžiaus) atvejis, kai diagnozuota inkstų akmenligė ir stebėti keli ūmaus inkstų pažeidimo epizodai. Pagrindinės priežastys, išprovokavusios ūmų inkstų pažeidimą, buvo atviras arterinis latakas, sepsis ir kaptoprilis. Vieno mėnesio pacientei nustatyti dešinio inksto kalcinatai, kurie per dvi savaites susiformavo į linijinius akmenis visoje kolektorinėje sistemoje. Smulkūs kalcinatai išliko dešiniajame inkste ir pusės metų amžiuje.

Išvada. Naujagimio, kuriam išsivysto ūmus inkstų pažeidimas, ištyrimas turi būti kompleksinis. Ankstyvas rizikos veiksnių identifikavimas, inkstų akmenligės prevencija, taip pat efektyvus gydymas gali sumažinti neišnešiotų naujagimių ūmių inkstų pažeidimų išsivystymo riziką.

Raktažodžiai: ūmus inkstų pažeidimas, inkstų akmenligė, neišnešiotas naujagimis