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# Clinical Features of Late-onset Circulatory Collapse in Preterm Infants

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**Purpose :** We aimed to describe the clinical features of late-onset circulatory collapse (LCC) in preterm infants.
**Methods** : The records of preterm infants with a gestational age of <33 weeks who were admitted to a single neonatal intensive care unit and survived more than 72 hrs between March 2006 and August 2012 were reviewed retrospectively.
**Results :** Of the total of 659 patients, 44 (6.7%) were diagnosed with LCC. Their mean gestational age was 26.0±1.9 weeks and their median birth weight 830 g. The median time of onset of LCC was 16.5 postnatal days. The patients exhibited oliguria that responded to hydrocortisone but not to hydration or catecholamines. Other clinical features of LCC were hypotension (73%), hyponatremia (52%), and hyperkalemia (34%). These abnormalities resolved in sequence: oliguria resolved first, after a median of 2.2 hrs, followed by hypotension after a median of 3.0 hrs, and the serum Na level became normal after 12.9 hrs. The incidence of LCC increased as the gestational age and/or birth weight decreased. A total of 26 patients (59%) developed LCC within 2 weeks after the initiation of levothyroxine therapy.
**Conclusions :** LCC in preterm infants was a relatively reversible condition but could be associated with severe morbidity. We therefore recommend the implementation of careful measures for early detection and prompt management of LCC, particularly after stressful events.

**Key Words :** Adrenal insufficiency, Hydrocortisone, Hypotension, Neonatal intensive care, Premature infant

Systemic hypotension is a common occurrence in preterm infants, affecting approximately one-third of very low birth-weight infants (VLBWIs) and associated with increased mortality and morbidity.[1,2] Low blood pressure usually results from hypovolemia, hemorrhage, myocardial dysfunction, or insufficient vasoconstriction.[3-5] In particular, corticosteroid-responsive hypotension among VLBWIs during the early postnatal period has been reported by several authors.[6-9] Some severely ill preterm infants have inadequate cortisol levels in the immediate postnatal period. These low cortisol levels are due to immaturity of the hypothalamic-pituitary-adrenal axis, which may impair the ability to release glucocorticoids in response to stress.[10-12] This adrenal insufficiency during the postnatal period is transient, and adrenal function usually returns to normal by the end of the second week of life.[13] However, many cases of late-onset circulatory collapse (LCC) have been reported in recent years, mainly in Japan. A Japanese nationwide survey reported that about 4% of VLBWIs may develop corticosteroid-responsive circulatory collapse beyond the first week of life.[14] They named this pathophysiology LCC. Although research suggests that this phenomenon results not from an absolute deficiency of cortisol production but possibly from a limited ability to synthesize sufficient cortisol under excess

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stress,[15] the mechanism of LCC has not been fully determined.

To date, most cases of LCC have been reported from Japan, while a few reports with limited numbers of VLBWIs with LCC have been published in the Republic of Korea.[16,17] Here, we focused specifically on description of the clinical course and the changes in sequence after corticosteroid treatment of LCC experienced in our neonatal intensive care unit (NICU). And we aimed to increase the general understanding of LCC.

## Materials and Methods

### 1. Patients

Between March 2006 and August 2012, a total of 2,410 infants born at Gachon University Gil hospital were admitted to the NICU and survived for more than 72 hrs. Of these, we retrospectively reviewed the medical records of 659 preterm infants who were delivered at less than 33 weeks of gestation.

### 2. Criteria for LCC

LCC was considered as a diagnosis in infants with acute-onset hypotension or oliguria that occurred in the context of a stable circulatory condition after the resolution of the immediate postnatal acute unstable circulatory state, usually after the 7th day of life. LCC was diagnosed if an infant showed oliguria (<1 mL/kg/h, <1/2 of the urine output of the previous 8-hrs interval during an 8-hrs interval, or anuria during a 4-hrs interval) in combination with at least 1 of the following clinical features: (1) systemic hypotension, diagnosed when the mean arterial pressure (MAP) remained less than 30 mmHg for at least 3 hrs; (2) hyponatremia, i.e., a serum sodium (Na) level less than 130 mEq/L; (3) hyperkalemia, i.e., a serum potassium (K) level greater than 6.0 mEq/L; or (4) hypoglycemia, i.e., a serum glucose level less than 60 mg/dL. Additionally, the diagnosis of LCC required that an infant who fulfilled the above criteria did not respond to volume expansion and/or catecholamines but did respond to corticosteroid injection. Infants who showed signs and symptoms of systemic infection (including a serum C-reactive protein (CRP) level greater than 0.5 mg/dL), symptomatic patent ductus arteriosus (PDA), bleeding, or necrotizing enterocolitis (NEC) were excluded because these clinical events could directly induce systemic hypotension and oliguria.

### 3. Measurement methods

The MAP was measured at least every 2 hrs by an oscillometric technique. The urine output was checked at least every 2 hrs. The serum concentrations of Na, K, and glucose were measured simultaneously when capillary blood gas analysis was required. The CRP level of venous blood was measured when required. Cranial ultrasonography was performed on the third and seventh days of life and weekly thereafter.

### 4. Data collection

We retrospectively reviewed the medical records of infants diagnosed with LCC and extracted the following data related to neonatal and perinatal characteristics: birth weight, gestational age, sex, multiple birth, Apgar scores at 1 and 5 minutes, Cesarean section, premature rupture of membranes (PROM), maternal hypertension, and maternal diabetes mellitus (DM). We also recorded the time of onset of LCC, whether dopamine or dobutamine was administered to treat the hypotension and/or oliguria, the interval of time between the onset of oliguria and the administration of hydrocortisone, and the duration of hydrocortisone treatment. The time of onset of oliguria and the time required to return to normal urination were also recorded. The MAP was recorded,

and if there was hypotension the time required to reach a MAP of >30 mmHg was noted. The serum concentrations of Na, K, and glucose were extracted from the blood gas analysis data, and the time required to reach a Na level of >130 mEq/L was also collected. To analyze the clinical events before the development of LCC, we examined the records regarding levothyroxine (LT4) administration, surgical ligation of PDA, thoracocentesis, seizures, and other such events. To analyze the outcomes and the prognosis of LCC, we reviewed the records for diagnoses of retinopathy of prematurity (ROP), periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH), intracerebral hemorrhage (ICH), necrotizing enterocolitis (NEC), and other such diseases. In addition, the causes of death of the infants who expired were determined from the medical records. Statistical analyses were performed using MedCalc 12.4.0.0 (MedCalc Software, Mariakerke, Belgium).

### 5. Definitions

Periventricular leukomalacia (PVL) was diagnosed by a single radiologist using cranial ultrasonography when the de Vries grading system score for cerebral leukomalacia was greater than grade 2.[18] Intraventricular hemorrhage (IVH) was diagnosed using cranial ultrasound by a neonatologist or radiologist, and the grade was assigned according to the classification used by Volpe.[19] NEC was defined according to Bell's criteria (≥ stage II).[20] Gastrointestinal perforation was diagnosed when radiography showed free air in the abdominal cavity. The term "preceding clinical events" was used to refer to events that occurred within 2 weeks before the appearance of LCC.

### 6. Ethical Approval

Ethical approval for the study was obtained from the clinical research ethics committee of the Gachon University Gil Hospital.

## Result

### 1. Characteristics of infants with LCC

During the study period, 44 infants were diagnosed with LCC. One infant with LCC had idiopathic hydrops fetalis and was delivered at 32 gestational weeks with a birth weight of 2,360 g. Among the remaining 43 patients, the median birth weight was 830 g (range 420 to 1,350 g) and the mean gestational age was 26.0±1.9 weeks (range 22.0 to 31.3 weeks). Twenty-eight of the 44 (63.6%) were boys. The median Apgar scores were 4 at 1 min and 7 at 5 min. The maternal characteristics included delivery by Cesarean section for 28 of the 44 infants (68%), PROM (14 of 44, 36%), maternal hypertension (4 of 44, 10%), and maternal DM (3 of 44, 8%).

### 2. Onset of LCC and characteristics of management

LCC developed a median of 16.5 days (range 5 to 158 days) after birth. The onset of LCC peaked between the 11$^{th}$ and 15$^{th}$ days and the majority of cases of LCC developed between the 6th and 40th days of hospitalization, as presented in Fig. 1. Intravenous hydrocortisone

**Table 1.** Major Vital Signs and Laboratory Findings of Infants with Late-Onset Circulatory Collapse

| | Total (N = 44) |
|---|---|
| Oliguria, n (%) | 44 (100%) |
| Hypotension, n (%) | 32 (73%) |
| Median MAP (mmHg), median (range) | 23 (16-29) |
| Hyponatremia, n (%) | 23 (52%) |
| Median Na concentration (mEq/L), median (range) | 125.5 (109.2-129.9) |
| Hyperkalemia, n (%) | 15 (34%) |
| Median K concentration (mEq/L), median (range) | 7.3 (6.3-8.3) |
| Hypoglycemia, n (%) | 1 (3%) |

Abbreviation: MAP, mean arterial pressure

rescue was required in all infants (loading dose, 3–5 $mg \cdot kg^{-1} \cdot day^{-1}$ usually starting with 3 $mg \cdot kg^{-1} \cdot day^{-1}$ of hydrocortisone, tapered by 1 $mg \cdot kg^{-1} \cdot day^{-1}$ daily over 3 days, but the duration of hydrocortisone treatment was variable depending on the conditions of the patients). Hydrocortisone therapy was initiated a median of 10.7 hrs (range 0 to 56 hrs) after the onset of oliguria. The median duration of hydrocortisone administration was 4 days (range 1 to 23 days). The majority of infants with LCC were also treated with catecholamines: 40 of 44 (91%) received dopamine (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and 26 of 44 (59%) were administered dobutamine (5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

### 3. Major vital signs and laboratory findings of infants with LCC

All 44 patients with LCC exhibited oliguria, as shown in Table 1. Hypotension was observed in 32 patients (73 %), and the median MAP was 23 mmHg (range 16 to 29 mmHg). Hyponatremia was detected in 23 patients (52%), and the median serum Na concentration was 125.5 mEq/L (range 109.2 to 129.9 mEq/L). Hyperkalemia occurred in 15 patients (34%), and the median serum K concentration was 7.3 mEq/L (range 6.3 to 8.3 mEq/L). Hypoglycemia manifested in only 1 case (3%).

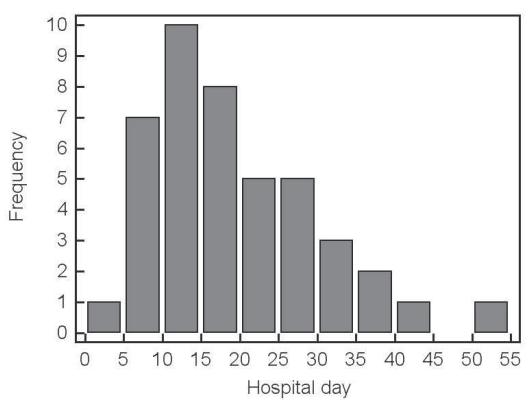


**Fig. 1.** Histogram of the onset of late-onset circulatory collapse showed that the onset peaked between the 11th and 15th days of life. The LCC developed between the 6th and 40th days of hospitalization in most cases.

### 4. Times required to recover from the clinical symptoms and signs of LCC

The administration of hydrocortisone to patients with LCC successfully relieved their clinical signs, such as oliguria, hypotension, and/or electrolyte imbalances, in all cases except for 2 patients who died within 2 days after the onset of LCC. Among the 42 patients who recovered, the oliguria resolved and normal urination resumed after a median of 2.2 hrs (range 0.5 to 24.0 hrs), as shown in Table 2. The MAP had returned to over 30 mmHg after a median of 3.0 hrs (range 0.5 to 41.3 hrs), and the serum Na concentration had increased to above 130 mEq/L after a median of 12.9 hrs (range 1.1 to 72.0 hrs).

### 5. Preceding clinical events before LCC

The clinical events that preceded the appearance of LCC are summarized in Table 3. Preceding clinical events refers to those events that occurred within 2 weeks before the appearance of LCC. These included LT4 administration in 26 of 44 (59%), surgical ligation of PDA in 8 of 44 (18%), and thoracocentesis in 3 of 44 (7%) patients. Three of 44 (7%) patients had a seizure before the onset of LCC. Other preceding clinical events in our patients with LCC were fetal hydrops (1 case) and a fracture of the tibia (1 case).

### 6. Morbidity and mortality of LCC

Twenty of 44 (45%) LCC patients later developed ROP of stage II or greater. PVL and IVH occurred in 7

**Table 2.** Hours to Recovery from Symptoms of Late-Onset Circulatory Collapse in the 42 Surviving Patients

| | Median (range) |
|---|---|
| Hours to normal urination | 2.2 (0.5-24.0) |
| Hours to MAP >30 mmHg | 3.0 (0.5-41.3) |
| Hours to Na concentration >130 mEq/L | 12.9 (1.1-72.0) |

Abbreviation: MAP, mean arterial pressure

of 44 (16%) patients each, and 4 of 44 (9%) patients had ICH. Four out of 44 (9%) suffered from NEC, and 2 of 44 (5%) had diaphragmatic palsy. Ten of our 44 (23%) patients with LCC expired before discharge from the hospital. Two of these died within 2 days after the diagnosis of LCC when the clinical symptoms and signs of LCC failed to resolve even in response to hydrocortisone. The causes of deaths were thought to be shock, oliguria, and respiratory insufficiency. The other patients expired from various causes in the hospital days after the recovery of LCC: 3 patients had sepsis, another 3 patients had NEC, 1 had disseminated intravascular coagulation, and the remaining infant had pneumothorax.

**Table 3.** Preceding Clinical Events before Late-Onset Circulatory Collapse

| | Total (N = 44) |
|---|---|
| LT4 administration, n(%) | 26 (59) |
| PDA ligation, n(%) | 8 (18) |
| Thoracocentesis, n(%) | 3 (7) |
| Seizure, n(%) | 3 (7) |
| Fetal hydrops, n(%) | 1 (2) |
| Fracture, n(%) | 1 (2) |

Abbreviations: LT4, levothyroxine; PDA, patent ductus arteriosus

### 7. Incidence of LCC with respect to gestational age and birth weight

We calculated the incidence of LCC in the 659 infants who were born in the hospital at a gestational age of less than 33 weeks, were admitted to the NICU, and survived more than 72 hrs. Forty-four of the 659 qualifying patients (6.7%) were diagnosed with LCC. The incidence of LCC increased as the gestational age decreased, as shown in Fig. 2, occurring in 9.1% at 28 weeks of gestation, 21.4% at 26 weeks, 33.3% at 24 weeks, and 66.7% at 22 weeks. Also the incidence increased as the birth weight decreased, occurring in 1.5% between 1,500g and 1,749 g, 3.9% between 1,000 g and 1,249 g, 17.0% between 750 g and 999 g, 24.1% between 500 g and 749 g, and 57.1% below 500 g.

### 8. Rates of survival of patients with LCC with respect to gestational age and birth weight

The overall survival rate of our patients with LCC was 77.3%, as shown in Fig. 3. As sorted by gestational weeks, survival rate was 60% in 28 weeks of gestation, 77.8% in 26 weeks of gestation, 71.4% in 24 weeks of gestation, 33.3% in 23 weeks of gestation, and 0% in 22

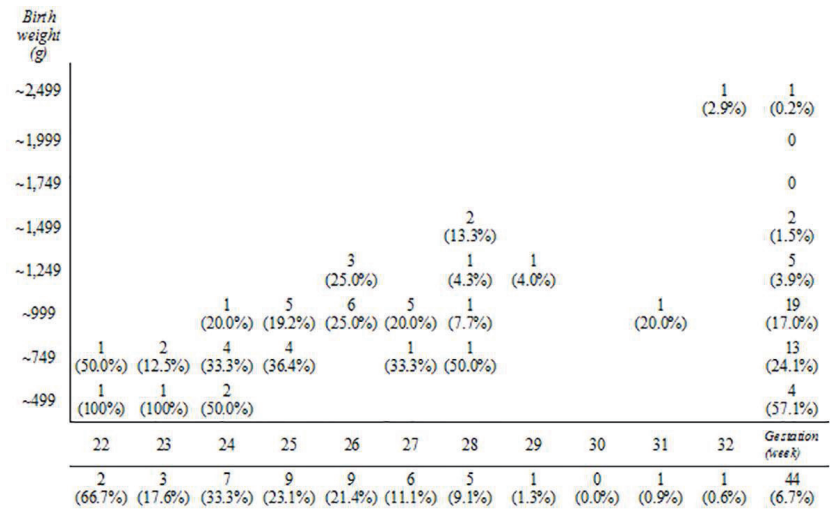


**Fig. 2.** The incidence of late-onset circulatory collapse increased as the gestational age decreased and the birth weight decreased.

weeks of gestation. There was no association between the survival rate and the gestational age. However, the survival rate were 89.5% in the group whose birth weight was between 750 g and 999 g, 76.9% between 500 g and 749 g, and 0% less than 500 g. The survival rate of patients with LCC tended to decrease as the birth weight decreased.

## Discussion

LCC is a condition specific to premature infants that is characterized by a sudden onset of cardiac dysfunction, including systemic oliguria and hypotension accompanied by hyponatremia or hyperkalemia, with no obvious cause, occurring after the stabilization of circulation and respiration beyond the first week of life and improving promptly in response to hydrocortisone.[21] To date, most studies of LCC have been reported from Japan, with only 2 reports concerning Korean infants.[16, 17] There are no definite diagnostic criteria for LCC and therefore independent guidelines are used for glucocorticoid treatment, with diagnostic criteria determined based on clinical observations. We used cut–off MAP values of 30 mmHg to define hypotension. LCC is usually occurred in extremely low birth weight infants (ELBWIs) and that cerebral blood flow is likely to be autoregulated above a breakpoint that averages 30 mmHg in ELBWIs.[22, 23] Therefore our cut–off value may be reasonable.

In this study, we found that about 6.7% of preterm infants born at <33 weeks of gestation were diagnosed with LCC according to the diagnostic criteria used in our hospital. This was consistent with the incidence rates in the previous Korean studies[16, 17] and was lower than that in a recent report from Japan.[21] However, the diagnostic criteria for LCC may vary among NICUs at different hospitals. Therefore, it is difficult to compare the incidence of LCC accurately among different studies.

The median birth weight of the 43 infants excluding the 1 patient with fetal hydrops was 830 g (range 420 to 1,350 g) and the mean gestational age was 26.0±1.9 weeks (range 22.0 to 31.3 weeks). The infant with fetal hydrops was included in the total number of patients with LCC because the combination of oliguria and hyponatremia appeared on postnatal day 15, after she had been stabilized and her fetal hydrops resolved.

In our patients, the incidence of LCC tended to increase as the gestational age and birth weight decreased, as

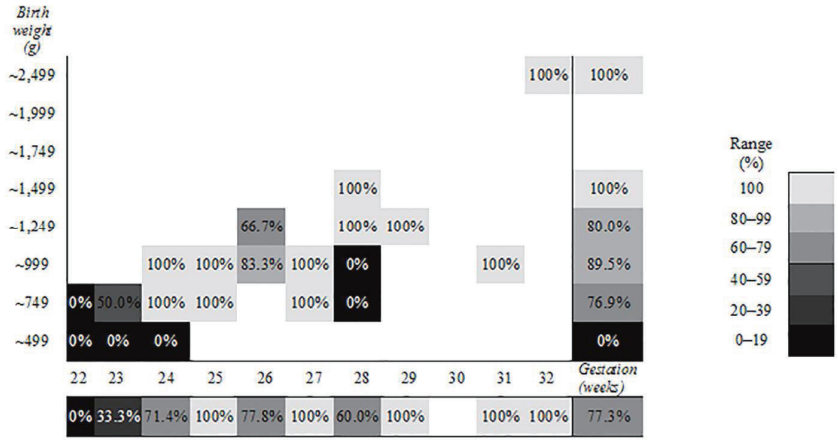


**Fig. 3.** There was no association between the survival rate of patients with late-onset circulatory collapse and the gestational age. The survival rate tended to decrease as the birth weight decreased.

shown elsewhere.[15, 21] These trends suggest that premature delivery may be an important risk factor for the development of LCC.

In this study, the median postnatal day of LCC onset was 16.5 days. Similarly, other studies have found that LCC usually develops between the second and third weeks of life.[17, 21, 24] The clinical features of LCC include hypotension, hyponatremia, hyperkalemia, and hypoglycemia, but not every feature manifested in every infant with LCC. Hypotension was the most common (73%) accompaniment to oliguria, but electrolyte imbalances sometimes occurred: hyponatremia appeared in 52% and hyperkalemia in 34% of patients with LCC. This heterogeneity of clinical features was observed in a previous report, although that study did not quantify the frequency of appearance of each abnormality.[25] Given these findings, we recommend close observation with suspicion of LCC for patients with oliguria and hypotension even in the absence of hyponatremia or hyperkalemia.

The median duration of hydrocortisone therapy in this study was 4 days (range 1 to 23 days). Most of the patients recovered dramatically from their oliguria, hypotension, and/or electrolyte imbalances after the administration of hydrocortisone. This suggests that LCC is a transient rather than a permanent condition and requires prompt management. Urination recovered first, followed by the mean arterial pressure and then the serum Na concentration. This implies that urination could be the most useful therapeutic landmark as it is like to be the first noticed by clinicians.

The causes and pathogenic mechanisms of LCC have not yet been determined. Severely ill preterm infants are known to have inadequate cortisol levels in the immediate postnatal period. Their inability to induce a surge of cortisol in response to stressful conditions might lead to a relative adrenal insufficiency rather than an absolute deficiency of cortisol production.[9] In our cases, LT4 administration was the event most frequently preceding the development of LCC. Twenty-six of 44 infants received LT4 before LCC developed, consistent with reports that LT4 induces LCC in preterm infants.[25-27] LT4 might cause stress by increasing cortisol metabolism and clearance. The other preceding events included PDA ligation, thoracocentesis, seizures, and fracture of a long bone. These stressful events could have increased the risk for LCC. The possibility of LCC must be considered after stressful events such as the initiation of LT4 therapy in vulnerable patients.

About 45% of the patients with LCC in this study developed ROP of stage II or greater, and there were also several neurological complications such as PVL, IVH, and ICH. As the doses of hydrocortisone used to treat LCC were within the physiological range, it is unlikely that the poor neurological outcomes arose from excessive use of hydrocortisone.[28] On the other hand, a small case-control study has suggested a significant association in preterm infants between late-onset PVL and late-onset circulatory collapse.[29] The pathogenesis of PVL in patients with LCC is thought to involve the remarkable decrease in cerebral blood flow and abnormality of cerebral hemodynamics during severe hypotenstion.[30] Therefore, such neurological complications as PVL more likely result from the LCC itself than from the hydrocortisone. At present, there is no effective treatment for neurological complications in preterm infants, making early detection and correction of hemodynamic disturbances in high-risk preterm infants are very important for the prevention of brain damage and reduction of disability. NEC manifested after the diagnosis of LCC in 7 of 44 infants, and 3 of them died from complications of NEC. Corticosteroids are known to be able to induce gastrointestinal perforation. However, the hypoperfusion that occurs during LCC

might be sufficient to cause longer ischemia in the intestine and thus be related to the development of NEC. Further studies are necessary to clarify the pathogenesis of NEC after LCC and the association between NEC and LCC. There were 10 deaths after the diagnosis of LCC was made, and the overall survival rate was 77.3 %. Among the patients with LCC who expired, 2 died with refractory hypotension and oliguria before the resolution of the LCC itself. It was not obvious whether these 2 patients represented a type of LCC that does not respond to steroids or whether they died because of other diseases that were not related to the LCC. Further investigation or additional reports on this potential corticosteroid–resistant type of LCC seem warranted.

The limitations of this study were, first, that the serum levels of cortisol and other hormones were not measured in each patient. It was therefore not possible to demonstrate the suspicious pathophysiological relationship between LCC and adrenal insufficiency. Second, there was no control group. We could not show the significance of the clinical features of infants with LCC in contrast to relatively stable preterm infants without LCC. Third, this was a single–center study, and the results cannot necessarily be generalized to other populations. Therefore, a multi–center study is recommended to establish more precisely the optimal diagnostic criteria and treatment strategy.

In conclusion, LCC was a relatively common condition among preterm infants and developed more frequently in those with lower gestational ages and birth weights. Although LCC is associated with severe mortality and morbidity, most patients recovered dramatically after corticosteroid treatment. We recommend close observation with suspicion of LCC in any patient with oliguria and hypotension after a stressful event such as LT4 administration. Early detection of LCC and prompt administration of hydrocortisone could improve the therapeutic outcome and prognosis of LCC. Further research is needed regarding the long–term prognosis of patients with LCC and the pathogenic mechanisms underlying it.

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## = 국 문 초 록 =

# 미숙아에서 만기순환부전의 임상 양상

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**목적 :** 이 연구는 미숙아에서 발생한 만기순환부전(late-onset circulatory collapse, LCC)의 임상 양상을 기술하고자 시행되었다.

**방법 :** 2004년 9월부터 2012년 8월까지 가천대 길병원 신생아집중치료실에 입원하였던 재태기간 33주 미만의 미숙아 중 72시간 이상 생존한 환아의 기록을 후향적으로 연구하였다.

**결과 :** 총 659명 중 LCC로 진단된 환아는 44명(6.7%)이었고, 평균 재태연령은 26.0주, 출생체중은 830 g이었다. 출생 후 16.5일에 증상이 발현되었고, 환자들은 수액투여 또는 강심제에 반응하지 않으면서 hydrocortisone에는 반응하는 핍뇨를 보였다. 그 외 저혈압(73%), 저나트륨혈증(52%), 고칼륨혈증(34%) 등이 동반되었다. Hydrocortisone 투여 후에는 가장 먼저 2.2시간 만에 핍뇨가 호전되었고, 3.0시간에 혈압이 상승하였고, 12.9 시간에 혈청나트륨이 정상화되었다. LCC의 발생은 재태기간이 짧을수록, 출생체중이 작을수록 많이 증가하였고, 총 26명(59%)의 환자에서 levothyroxine의 투여시작 후 2주 내에 발생하였다.

**결론 :** 미숙아에서 LCC는 가역적으로 회복될 수 있는 상태이지만, 심각한 합병증을 일으킬 수도 있다. 따라서 스트레스 상황 후에는 LCC를 조기에 진단하고 신속하게 치료할 수 있도록 주의를 기울여야 한다.

**중심 단어 :** 부신기능부전, Hydrocortisone, 저혈압, 신생아 집중 치료, 미숙아