Late-Onset Glucocorticoid-Responsive Circulatory Collapse in Preterm Infants: Clinical Characteristics of 14 Patients

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Preterm infants may develop acute systemic hypotension that responds to glucocorticoid therapy, but not to volume loading or vasopressors, during the immediate postnatal period. These infants receive glucocorticoid therapy to maintain the target blood pressure defined by each institution. It is currently unclear whether the acute shock associated with this condition results in neurological sequelae or other morbidities (Bourchier and Weston 1997; Ng et al. 2004, 2006; Efird et al. 2005).

It has recently been reported that some preterm infants develop acute profound primary circulatory failure that responds to glucocorticoid therapy, but not to volume expansion or vasopressors, after the first week of life. This condition is termed late-onset circulatory collapse (LCC) if other causes of circulatory failure such as sepsis, patent ductus arteriosus, and hemorrhage are excluded (Nakanishi et al. 2010; Kawai et al. 2012).

The pathophysiological mechanism underlying LCC is thought to be relative adrenal insufficiency (Masumoto et al. 2008). Levothyroxine replacement has been implicated as one of the factors that provoke LCC (Takizawa et al. 2010; Yagasaki et al. 2010; Kawai et al. 2012). Cardiac and organ flow patterns on echography suggest distributive shock (Washio et al. 2013). Moreover, LCC is an obvious risk factor in the development of periventricular leukomalacia (PVL), because of the severe deterioration that occurs during disease onset (Kobayashi et al. 2006; Nakanishi et al. 2010).

Currently, even the clinical features of LCC remain poorly understood. Ours is the first reported case series that provides a comprehensive description of the diagnostic clues and clinical features of LCC, including a detailed history of prenatal betamethasone, serum cortisol levels in the umbilical artery, physical findings and blood glucose and hormone levels at onset, the time from the initial hydrocortisone dose to improvement, and the total period and dose of hydrocortisone needed to achieve a positive response. We show that in the management of LCC it is important to stabilize the patient’s circulation with the appropriate administration of glucocorticoids, to reduce the risk of

Keywords: adrenal insufficiency; hyponatremia; hypotension; oliguria; periventricular leukomalacia

*Methods*

Infants treated for LCC at Saiseikai Yamagata Saisei Hospital (a tertiary care perinatal facility) were included in this study. No infants developed LCC beyond 29 weeks of gestational age (GA). Between June 2010 and July 2014, 41 infants less than 29 weeks of GA were admitted to our hospital, 15 of whom were treated for LCC. Infants with congenital heart disease, multiple anomalies, and twin to twin transfusion syndrome were excluded. One infant was excluded from the study because some of the echographic findings and laboratory data were lost.

LCC is defined as the acute onset of hypotension or oliguria occurring after the first week of life and requiring multiple doses of hydrocortisone for several days or longer to maintain circulation. We defined hypotension as a decrease in systolic blood pressure of 15%, and oliguria as a decrease in the 8-h urine output of 50%. LCC was diagnosed after the exclusion of systemic infection, primary cardiac or renal failure, hemorrhage, sudden anemia, hypocalcemia, hypothyroidism, or glucocorticoid withdrawal as the cause of cardiovascular failure (Mao et al. 2007; Maiya et al. 2008). We reconfirmed whether all the cases matched the definition.

The study protocol was approved by the Institutional Review Board. Medical records were retrospectively reviewed and blood pressure, urine volume, skin color, respiratory status, physical activity, and laboratory data at the time of diagnosis of LCC were recorded. Maternal factors considered in this study were perinatal corticosteroid therapy, pregnancy-induced hypertension, and pathologic chorioamnionitis. Neonatal factors were GA at delivery, sex, birth weight, and Apgar scores. Pre- and post-LCC histories of necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) or PVL, late-onset sepsis, retinopathy of prematurity, chronic lung disease (CLD), and postnatal glucocorticoid administration were also evaluated.

All very low birth weight infants routinely underwent functional echocardiography and organ blood flow Doppler studies more than once a day until about 1 month after birth and at the time of suspected LCC. The examination was carried out using a Philips SONOS 5500 system (Andover, MA). Left ventricular fractional shortening (LVFS), left ventricular internal dimension at end-diastole (LVIDd), and resistance index (RI) in the renal and anterior cerebral arteries were routinely assessed. Blood pressure, urine volume, serum-levels of electrolytes, and blood glucose, and ultrasonographic findings were compared average of 2-5 days before and after the onset of LCC. Urine output during the 8 h before diagnosis of LCC was recorded.

To prevent IVH, fentanyl (0.3-0.8 μg/kg/h) was administered during the first days after birth in infants born at a GA of < 29 weeks, as described by Toyoshima et al. (2013). The mean systemic blood pressure (mmHg) was maintained above the number of weeks of GA. If the systemic blood pressure dropped below this level, hydrocortisone was administered. If the response to hydrocortisone administration was inadequate, volume loading and dopamine were also provided. No other medications were routinely administered other than enteral *Lactobacillus casei*. Low-dose hydrocortisone therapy at a dose below the previously reported prophylactic one was administered when the required fraction of inspired oxygen was consistently > 0.6 (Watterberg et al. 1999). No glucocorticoids other than hydrocortisone were used. Patent ductus arteriosus was treated with cycles of three doses of indomethacin (0.1 mg/kg at 12- to 24-h intervals) with at least 1 week between cycles.

The data are expressed as the median and interquartile range (IQR) or as the range unless stated otherwise. Statistical analyses were performed using SPSS software, version 22 (IBM, Armonk, NY).

*Results*

**Perinatal factors**

Fourteen infants with LCC were identified. Patient 3 was one of monozygotic twin brothers, and patients 5 and 6 were dizygotic twin sisters. The median GA at birth was 26 weeks (IQR 25-27 weeks) and the median birth weight was 736 g (IQR 691-797 g) (Table 1). Fentanyl was administered from birth for a median time of 5 days (range 3-8 days). In eight of the infants, a single dose of hydrocortisone was administered between 3 and 11 h after birth to increase blood pressure. After this single dose of hydrocortisone, there was no need for volume loading or vasopressors for blood pressure maintenance. Hydrocortisone was administered to five infants (patients 1, 3, 7, 8, and 10) to improve respiration. All infants with patent ductus arteriosus received indomethacin. Methylxanthine was administered to ten infants and levothyroxine to one infant. At the time of LCC diagnosis, none of the infants received diuretics or had life threatening infections or histories of asphyxiation.

**Characteristics at the time of LCC diagnosis**

LCC developed at a median age of 21 days (IQR 18-32 days) (Table 1). At the time of diagnosis, breast milk intake was 130 mL/kg/day (IQR 121-136 mL/kg/day), total water intake was 155 mL/kg/day (IQR 136-160 mL/kg/day), and sodium (Na+) intake excluding milk was 6.2 mEq/kg/day (IQR 5.1-8.2 mEq/kg/day). All infants had a relatively stable respiratory status aided by tracheal intubation and mechanical ventilation, except for one infant (patient 11) who received nasal continuous positive airway pressure ventilation. All infants were in a relatively stable condition without prodromal signs at the time of LCC onset. In five infants (patients 5, 7, 10, 13, and 14), LCC developed 6-8 h after the periodic ophthalmologic examination of the fundus.

Most infants had no urine output for several hours prior to diagnosis. Physical activity decreased at the time of LCC diagnosis in all infants. There was no increase in apneas or increased need for ventilatory support. None of the infants developed pigmentation or severe edema, but 8 of the 14 infants had a slightly pale skin color. All infants had a normal intake of enteral breast milk, a stable temperature, a normal complete blood count, normal serum levels of creatinine and calcium, and a C-reactive protein level of < 0.3 mg/dL. Three infants (patients 3, 5, and 9), developed hyperkalemia (K+ > 6 mEq/L) at the time of diagnosis (Fig. 1).

Echocardiography at the time of diagnosis showed patent ductus arteriosus in two infants (patients 1 and 13), but
Table 1. Clinical characteristics during the perinatal period and at the time of LCC diagnosis.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>GA (weeks)</th>
<th>BW (g)</th>
<th>Sex</th>
<th>Apgar at 1/5 min</th>
<th>CAM (stage)</th>
<th>PIH</th>
<th>Prenatal betamethasone (mg) (time before delivery)</th>
<th>Serum cortisol at umbilical artery (μg/dL)</th>
<th>Total HC dose prior to LCC (mg/kg)</th>
<th>Events before LCC onset</th>
<th>Corrected GA at LCC onset</th>
<th>Data at LCC onset</th>
</tr>
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<td>1</td>
<td>24.0</td>
<td>690</td>
<td>M</td>
<td>7/8</td>
<td>2</td>
<td>Yes</td>
<td>12 (1 day)</td>
<td>&lt; 0.1</td>
<td>1.7</td>
<td>IVH (grade 3), NEC (stage 3), jejunostomy</td>
<td>27.0</td>
<td>10.4 1.5 328</td>
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<td>24.3</td>
<td>742</td>
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<td>32.4</td>
<td></td>
<td></td>
<td>34.8 1,240</td>
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<td>692</td>
<td>M</td>
<td>6/8</td>
<td>2 No</td>
<td></td>
<td>24 (6, 7 days)</td>
<td>2.7</td>
<td>3.4</td>
<td>IVH (grade 3), PPHN, pleural effusion</td>
<td>26.3</td>
<td>11.9 16.2 491</td>
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<td>24.6</td>
<td>732</td>
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<td>28.1</td>
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<td></td>
<td>5.8 1,340</td>
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<td>585</td>
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<td>1.3</td>
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<td></td>
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<td>814</td>
<td>M</td>
<td>4/7</td>
<td>No No</td>
<td></td>
<td>24 (2, 3 days)</td>
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<td>1.0</td>
<td></td>
<td></td>
<td>27.6 836</td>
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<td>944</td>
<td>F</td>
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<td>5.3</td>
<td></td>
<td></td>
<td>30.3 185</td>
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<td>27.3</td>
<td>740</td>
<td>M</td>
<td>9/9</td>
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</tr>
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<td>12</td>
<td>27.7</td>
<td>640</td>
<td>M</td>
<td>3/5</td>
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<td>24 (1, 2 days)</td>
<td>1.8</td>
<td>0</td>
<td>Heart failure, IVH (grade 2)</td>
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<td>27.7</td>
<td>1,043</td>
<td>F</td>
<td>7/8</td>
<td>No No</td>
<td></td>
<td>24 (9, 10 days)</td>
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<td>0</td>
<td></td>
<td></td>
<td>31.3 16.5 8.7 1,600</td>
</tr>
<tr>
<td>14</td>
<td>28.1</td>
<td>858</td>
<td>F</td>
<td>7/8</td>
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<td>24 (5, 6 days)</td>
<td>2.6</td>
<td>0</td>
<td></td>
<td></td>
<td>30.6 8.6</td>
</tr>
</tbody>
</table>

GA, gestational age; BW, birth weight; M, male; F, female; CAM, chorioamnionitis; PIH, pregnancy-induced hypertension; HC, hydrocortisone; LCC, late-onset circulatory collapse; IVH, intraventricular hemorrhage (Papile grade); NEC, necrotizing enterocolitis (Bell’s stage); ACTH, adrenocorticotropic hormone; PPHN, persistent pulmonary hypertension of the newborn.
no exacerbation of shunt flow. There were no significant changes in LVIDd or LVFS. Doppler ultrasonography showed an increased RI in the anterior cerebral artery and in the renal artery (Fig. 1).

**Therapy and clinical course**

The initial dose of hydrocortisone was 2-5 mg/kg, in reference to a previous report (Nakanishi et al. 2010) (Table 2). A volume load of normal saline (10-30 mL/kg) was administered at the same time in all except four infants. In patient 5, blood pressure and urine output improved after 15 h; hydrocortisone at a dose of 2 mg/kg was added after 5 h, followed by 3 mg/kg 5 h thereafter (Table 2). The hydrocortisone dose was reduced as early as possible while making sure that there was no decrease in physical activity, blood pressure, or urine output and no increase in RI in the renal artery. Indeed, a dose increase was often needed when recurrence developed following a hasty dose reduction. The duration of hydrocortisone therapy was 23 days (IQR 14-30 days). The total dose of hydrocortisone administered was 34.9 mg/kg (IQR 13.6-45.4 mg/kg) (Table 2).

**Prognosis**

The 17-hydroxyprogesterone concentration at the approximate expected due date was normal. One infant (patient 10) developed pneumonia while receiving hydrocortisone therapy. There were no deaths during the observation period, and no adverse effects related to hydrocortisone therapy. Patient 3 developed NEC (Bell’s stage 3) and bilateral mild IVH 5 weeks after the diagnosis of LCC. There was no evidence of PVL on imaging examinations at a corrected GA of 40 weeks in any of the infants (Table 2). CLD and retinopathy of prematurity, discharge day, and mental and physical development during the follow-up period (median 2.5 years) were similar to those of infants who did not develop LCC (Table 2). None of the infants developed adrenal insufficiency after the end of treatment for LCC.

**Discussion**

This study describes 14 preterm infants who developed acute-onset circulatory failure that responded to glucocorticoid therapy. Other causes of circulatory failure were ruled out.

LCC is defined as the acute onset of hypotension or oliguria that occurs after the first week of life. This condition has been reported mainly in Japan, where the incidence varies widely between different centers (Kusuda et al. 2006). A nationwide survey in Japan reported a prevalence of LCC of 11.6% in extremely low birth weight infants and
Late-Onset Circulatory Collapse in Preterm Infants

Table 2. Therapy, clinical course, and outcome.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Initial HC dose (mg/kg)</th>
<th>Recovery time after first HC dose (hours)</th>
<th>Total HC dose after diagnosis of LCC (mg/kg)</th>
<th>Duration of HC therapy after diagnosis of LCC (days)</th>
<th>Discontinuation of O₂, corrected GA (weeks)</th>
<th>ROP (stage/photocoagulation)</th>
<th>Discharge, corrected GA (weeks)</th>
<th>Brain MRI or CT at about the expected due date</th>
<th>Follow-up period (months)</th>
<th>Mental and physical development</th>
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<td>4</td>
<td>33</td>
<td>23</td>
<td>27.3</td>
<td>2 / Yes</td>
<td>43.0</td>
<td>Normal</td>
<td>22</td>
<td>Speech delay</td>
</tr>
<tr>
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<td>1.3</td>
<td>5</td>
<td>7</td>
<td>13</td>
<td>37.7</td>
<td>3 / Yes</td>
<td>Transferred to another hospital</td>
<td></td>
<td>4</td>
<td>Unknown</td>
</tr>
<tr>
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<td>4.3</td>
<td>3</td>
<td>121</td>
<td>67</td>
<td>Continued</td>
<td>3 / Yes</td>
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<tr>
<td>4</td>
<td>2.2</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>44.1</td>
<td>3 / Yes</td>
<td>52.1</td>
<td>Hydrocephalus, white matter abnormality</td>
<td>49</td>
<td>Speech delay, spastic diplegia</td>
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<td>15</td>
<td>79</td>
<td>30</td>
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<td>1 / No</td>
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<td>19</td>
<td>18</td>
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<td>White matter abnormality</td>
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<td>44.4</td>
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<td>White matter abnormality</td>
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<td>5.0</td>
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<td>30</td>
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<td>41.6</td>
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<td>44.4</td>
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HC, hydrocortisone; LCC, late-onset circulatory collapse; ROP, retinopathy of prematurity; MRI, magnetic resonance imaging; CT, computed tomography; PVL, periventricular leukomalacia; VP, ventriculoperitoneal; IVH, intraventricular hemorrhage (Papile grade); NEC, necrotizing enterocolitis (Bell’s stage).

†The initial dose of hydrocortisone was 2 mg/kg. Hydrocortisone at a dose of 2 mg/kg was administered after 5 h, and then at a dose of 3 mg/kg 5 h thereafter.
Previously reported studies found that LCC occurred in infants with a birth weight of < 1,000 g or GA at birth of < 30 weeks, and started 2-3 weeks after birth. Hypotension was associated with hyponatremia and a tendency towards hyperkalemia (Nakanishi et al. 2010). Infants with LCC had a high rate of PVL (Kobayashi et al. 2006; Nakanishi et al. 2010).

The pathophysiological mechanism underlying LCC is thought to be relative adrenal insufficiency, because the circulatory failure responds to glucocorticoid therapy but not to volume loading or vasopressors (Masumoto et al. 2008). LCC may result from the suppression of fetal cortisol production until late in the gestational period by interaction between the fetal hypothalamic-pituitary-adrenal axis and the placenta (Mesiano and Jaffe 1997; Kapoor et al. 2006). However, infants who develop LCC usually do not require more than a single dose of glucocorticoid to maintain their blood pressure during the first few days after birth. It is not clear why LCC develops a few weeks after birth in relatively stable infants.

Previously reported relative adrenal insufficiency in preterm infants can be classified into three types. The first type is glucocorticoid-responsive hypotension that occurs soon after birth (Bourchier and Weston 1997; Ng et al. 2004, 2006; Efird et al. 2005). It is thought to reflect an increased need for cortisol during the adaptation to extrauterine life. In the first few post-natal days, corticotropin-releasing hormone (CRH) stimulation tests show a normal adrenocorticotropic hormone (ACTH) level and a low cortisol level (Ng et al. 2004). Although there is no clear consensus regarding blood pressure management in preterm infants, the mean blood pressure is usually maintained above the number of weeks of GA (Levene et al. 1992; Dempsey and Barrington 2006; Dempsey et al. 2009). Previous studies reported the use of glucocorticoids to maintain the target blood pressure determined by each institution. Infants treated accordingly did not have hypotension or oliguria as defined above and were not at an increased risk of developing PVL, as occurs in patients with LCC. The second type of adrenal insufficiency is circulatory failure caused by various mechanisms, which may also respond to glucocorticoid therapy (Helbock et al. 1993; Noori et al. 2006). A diagnosis of LCC requires the exclusion of other causes of hypotension. The third type is relative hypotension secondary to the treatment of CLD (Yeh et al. 1997; Stark et al. 2001). Infants with CLD thought to be caused by adrenal insufficiency were reported to have a decreased ability to produce cortisol (Watterberg et al. 2001). However, the clinical findings were not consistent with typical adrenal insufficiency (Yeh et al. 1997; Stark et al. 2001; Watterberg et al. 2001). The characteristics of LCC differ from these three types of relative adrenal insufficiency.

Serum cortisol levels in preterm infants change in accordance with the general clinical condition, as is the case in adults (Heckmann et al. 1999; Cooper and Stewart 2003). However, in preterm infants both GA and the time since birth play additional roles (Huysman et al. 2000; Watterberg et al. 2001). In our patients, LCC did not appear to be caused by primary adrenal insufficiency, because plasma ACTH and serum cortisol levels were unremarkable. Ideally, randomly measured ACTH and cortisol levels at onset of LCC should be assessed to establish the differential diagnosis of overt primary adrenal insufficiency in all cases. However, it is important to diagnose LCC based on clinically available findings and to promptly administer hydrocortisone to reduce the risk of PVL rather than wait for the result of hormonal data because hormonal data is not obtained immediately. Furthermore, in adult cases, many threshold levels have been proposed for the definition of an insufficient cortisol level during acute illness, but none is entirely satisfactory (Cooper and Stewart 2003). Therefore, the exact diagnosis of relative adrenal insufficiency in especially very preterm infants may be difficult if complete data are obtained.

Infants in this study had mild hyponatremia at the time of LCC diagnosis and their serum Na⁺ levels often decreased further following the administration of normal saline. It was not possible to distinguish between changes due to Na⁺ loss and those due to dilution, but the latter is more likely because both serum Na⁺ level and urine output were maintained until the onset of LCC. A small number of infants developed hyperkalemia, but most did not have a significant change in serum K⁺ levels. The majority of the infants were dependent on enteral feeding, and none developed profound hypoglycemia. The decreased blood glucose level appeared to be due to late feeding following the performance of diagnostic procedures. Serum levels of Na⁺, K⁺, and glucose were similar to those of children with adrenal crisis due to adrenal insufficiency (Hsieh and White 2011).

Ultrasonographic examination showed increased RI associated with a decreased diastolic flow in the cerebral and renal arteries. In such cases, vascular resistance may be high (Tublin et al. 2003). These changes were not caused by a patent ductus arteriosus and were reversed by corticosteroid therapy (Lipman et al. 1982). Washio et al. (2013) reported similar findings and speculated that infants diagnosed with LCC had a constriction in a main peripheral artery that maintained blood pressure. In our study, the finding of absent or negligible diastolic flow in the renal arteries was a sensitive indicator of LCC and useful in its diagnosis.

Previous studies reported high rates of PVL in infants with LCC (Kobayashi et al. 2006; Nakanishi et al. 2010). We administered early glucocorticoid therapy in patients with hypotension and oliguria without giving priority to volume loading or inotropic support, based on our experience with the diagnosis of LCC and because the early reversal of circulatory failure appears to reduce the risk of PVL. The median time from the initial hydrocortisone dose
to the improvement of blood pressure and urine output was 4 h (IQR 3-5 h). Some infants required hydrocortisone doses that exceeded physiological cortisol replacement during the first few days after the diagnosis of LCC.

Detailed therapeutic information on the acute phase of LCC was not previously available. Our results show that if there is still no response 5 h after the last hydrocortisone dose, additional administration is recommended. There were large individual differences in the therapeutic period and total dose of hydrocortisone, suggesting the need for infant-specific treatment.

Our study had several limitations. Hormone levels were not routinely measured, especially in anemic infants, nor were CRH or ACTH stimulation tests performed. In the acute stage of LCC, the main priority is the early initiation of glucocorticoid therapy. A switch from hydrocortisone to dexamethasone therapy for a stimulation test should be avoided, because dexamethasone is associated with a higher risk of adverse neurological events (Stark et al. 2001; Karemaker et al. 2006). A detailed discussion of the etiology of LCC is beyond the scope of this article, but in addition to assessment of complete hormonal data at onset, CRH or ACTH stimulation tests should be performed to reveal the pathophysiology of LCC. Furthermore, we did not study the risk factors for LCC development and prognosis by comparing our data with those from non-LCC infants, because our focus was on describing the clinical features of LCC.

In conclusion, LCC is characterized by the acute onset of cardiovascular failure in preterm infants after a few weeks of life. It is associated with hyponatremia and increased RI in the cerebral and renal arteries, as demonstrated on Doppler ultrasonography. Some infants with LCC develop hyperkalemia. Well-preserved LVFS and LVIDd, an absence of skin pigmentation, and hypoglycemia are also characteristic of LCC. The median time from the initial hydrocortisone dose to improvement was 4 h. When the response of an infant with LCC is inadequate, an early additional dose of hydrocortisone is needed. If an appropriate circulatory state is maintained by the prompt and adequate administration of hydrocortisone, LCC does not seem to have a substantial effect on the neurological prognosis. However, the accumulation of a higher number of reported cases and longer observation periods are necessary to further evaluate the long-term effects of LCC and glucocorticoid therapy.

**Conflict of Interest**

The authors declare no conflict of interest.

**References**


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