




## Original Article

# Corticotrophin-releasing hormone stimulation tests in late-onset circulatory collapse

Hiroko Ueda,<sup>1</sup> Hiroki Kakita,<sup>1</sup>  Shintaro Ichimura,<sup>1</sup> Mari Mori,<sup>1</sup> Satoru Takeshita,<sup>1</sup> Tatenobu Goto,<sup>1,2</sup> Tomoko Kondo<sup>1</sup> and Yasumasa Yamada<sup>1</sup>

<sup>1</sup>Department of Perinatal and Neonatal Medicine, Aichi Medical University, Nagakute, Aichi and <sup>2</sup>Department of Pediatrics, Yokkaichi Municipal Hospital, Yokkaichi, Mie, Japan

**Abstract** **Background:** Late-onset circulatory collapse (LCC) is the transient development of refractory hypotension and oliguria after the early neonatal period, which may cause periventricular leukomalacia (PVL). The aim of this study was to evaluate the endogenous cortisol response to corticotrophin-releasing hormone (CRH) and determine whether it is effective for elucidating the pathology and selecting treatment in LCC.

**Methods:** This retrospective study examined infants admitted to the neonatal intensive care unit. Included were preterm (gestational age <34 weeks) infants who underwent CRH stimulation test and were treated for LCC with no obvious cause. Hydrocortisone (HC; 3.3–10 mg/kg) was given by bolus injection to the LCC infants. At 2 h after treatment, infants without a 20% rise in blood pressure (systolic or mean) from before treatment were defined as non-responsive to HC, and given catecholamine and/or vasopressin.

**Results:** Sixteen infants (median gestational age, 24 weeks 3 days; birthweight, 638 g) were eligible. Six of the infants had a good response to the CRH stimulation test. HC was effective in only three CRH good-response cases, and catecholamine and/or vasopressin was needed in the three other cases. HC was effective, however, for all CRH non-response cases.

**Conclusions:** Although HC is the first-choice treatment for LCC, the CRH stimulation test facilitates prompt treatment of LCC, which may prevent PVL. The present findings help elucidate the pathology and aid in the selection of treatment for infants with LCC.

**Key words** adrenocortical insufficiency, corticotrophin-releasing hormone stimulation test, hydrocortisone, late-onset circulatory collapse, preterm infant.

Late-onset circulatory collapse (LCC) is the transient development of refractory hypotension and oliguria after the early neonatal period. In a national survey in Japan, 6.3% of very low-birthweight (VLBW) infants and 11.6% of extremely low-birthweight (ELBW) infants developed LCC.<sup>1,2</sup> Typically, infants stabilized in a few days develop sudden onset of circulatory collapse after the early neonatal period.<sup>1</sup> LCC is usually resistant to inotropic drugs and volume expanders, but a physiologic dose of glucocorticoid is effective in most cases.<sup>1</sup> Good response to hydrocortisone (HC) suggests that LCC is caused by relative adrenal insufficiency. Ng *et al.* suggested that VLBW infants usually achieve normal adrenal function by the end of the second week of life, and that VLBW infants are prone to life-threatening hypotension secondary to adrenal

insufficiency.<sup>3,4</sup> The onset of most cases of LCC, however, is reported to be after the second week of life.<sup>1</sup> In addition, several reports noted that HC is not effective, and such LCC cases are sometimes caused by diuretics, and levothyroxine treatment.<sup>5,6</sup> The cause of LCC may be due not only to adrenal insufficiency, and the underlying pathology of LCC remains unclear.

Late-onset circulatory collapse occurs at the most vulnerable time for white matter injury and may cause periventricular leukomalacia (PVL), which is the most importance cause of cerebral palsy in VLBW infants. Development of LCC is a major risk factor of PVL.<sup>7,8</sup> This suggests that LCC is a serious event, and it is necessary to improve hypotension immediately, especially when glucocorticoid therapy is ineffective.

In this report, cortisol production in response to corticotrophin-releasing hormone (CRH) stimulation tests was examined in infants with LCC. The aim of this study was to evaluate the endogenous cortisol response to CRH and determine whether it is effective for elucidating the pathology and selecting treatment in LCC.

Correspondence: Hiroki Kakita, MD PhD, Department of Perinatal and Neonatal Medicine, Aichi Medical University, 1-1 Yazako, Karimata, Nagakute, Aichi 480-1195, Japan. Email: hkaki1019@yahoo.co.jp

Received 7 February 2019; revised 25 June 2019; accepted 4 July 2019.

## Methods

This was a retrospective study of infants who were admitted to the neonatal intensive care unit (NICU) from April 2013 to September 2018. Inclusion criteria for the study were prematurity (gestational age, <34 weeks), CRH stimulation test, and treatment for LCC. Infants with congenital malformation, congenital heart disease except patent ductus arteriosus (PDA), and chromosomal abnormalities, were excluded. This study was approved by the ethics committee of Aichi Medical University Hospital (institutional review board number :2015-H221). LCC was defined as the sudden onset of hypotension and/or oliguria resistant to volume expanders and inotropes after a stable period. There could be no obvious cause for the onset of hypotension or oliguria, such as sepsis, PDA, hypovolemia, intraventricular hemorrhage, or necrotizing enterocolitis. The resistant state to volume expanders and inotrope was defined on chest X-ray, echocardiography, and blood examination without actual treatment. Hypotension was defined as repeated blood pressure measurement <80% of the mean value prior to onset. Oliguria was defined as the presence of at least one of the following: (i) passing <50% of the previous 8 h urine volume over the subsequent 8 h period; (ii) passing <1 mL/kg/h of urine over the past 8 h period; or (iii) anuria during the past 4 h.<sup>1</sup>

Antenatal and intrapartum factors were evaluated, as follows: gestational age, birthweight, Apgar scores at 1 and 5 min, arterial or venous gases, pH, base excess, hematocrit at birth; sex, preterm rupture, mode of delivery, small for gestational age (weight <10th percentile of bodyweight for gestational age), multiple gestations, placental disruption, antenatal glucocorticoid therapy, preterm rupture of the membranes, and chorioamnionitis (CAM). CAM was defined as infection/inflammation of the membranes diagnosed on microbiology and histology. Postnatal data included age at onset, corrected gestational age at onset, duration of ventilation, duration of oxygen treatment; surfactant therapy, indomethacin therapy, glucocorticoid, diuretics, methylxanthine, caffeine, levothyroxine before onset, transfusion of red blood cells, erythropoietin therapy, total parenteral nutrition including lipid infusion, iron treatment, apnea, and retinopathy of prematurity. Apnea was defined as any complete cessation in breathing movements lasting >20 s. Retinopathy of prematurity was defined as the need for laser therapy.

For the CRH stimulation test in this study, the original method by Ng *et al.*<sup>4</sup> was modified. All tests were performed between onset and HC replacement. Serum cortisol was measured before and 30 min after bolus injection of human CRH (1 µg/kg; Tanabe, Tokyo, Japan). For the measurement of serum cortisol, a 300 µL blood sample is needed, and it takes 2 h at the latest from the second blood sampling to obtain the result. Serum cortisol was drawn from the i.v. line in all cases. A good response was defined as serum cortisol level after the bolus injection 1.5-fold that before, and/or serum cortisol >15 µg/dL after the bolus injection, according to the standard value.<sup>4</sup>

At the present institution we selected HC without supplemental catecholamine as the first-line treatment for LCC after having confirmed absence of abnormal cardiac volume and function. In the case of resistance to first-line treatment, supplemental catecholamine and subsequent vasopressin are considered. HC (3.3–10 mg/kg) was given to the LCC infants by bolus injection. At 2 h after treatment, infants without a 20% rise in blood pressure (systolic or mean) from before treatment were defined as non-responsive to HC, and were given vasopressin and/or catecholamine.

Magnetic resonance imaging was performed in all cases to confirm the diagnosis of PVL at discharge or at a corrected age of 40 weeks.

## Statistical analysis

Statistical analysis was performed using SPSS for Windows version 13.0 (SPSS, Chicago, IL, USA). Mann–Whitney *U*-test or Student's *t*-test was used to compare continuous data. The chi-squared test or Fisher's exact test was used to compare dichotomous outcomes. Data are reported as median (range) unless otherwise specified. *P* < 0.05 was considered significant.

## Results

A total of 297 preterm infants of gestational age <34 weeks were admitted to the NICU. Of these infants, 23 (7.7%) were diagnosed with LCC. Of the 23 LCC infants, seven were excluded because of congenital malformation, critical congenital heart disease, and death, given that it was impossible to perform the CRH stimulation test. Thus, a total of 16 infants were eligible for this study. We confirmed that all LCC infants had normal cardiac volume and function, and no obvious cause of hypotension and oliguria, on chest X-ray, echocardiography and blood examination.

The median gestational age and birthweight were 24 weeks 3 days (range, 23 weeks 1 day–30 weeks 2 days) and 638 g (range, 577–1,318 g), respectively. Of the 16 infants, six had a good response to the CRH stimulation test. With regard to time from the onset of LCC to the end of CRH stimulation test, there were no significant differences between the good (median, 1.25 h; range, 0.5–2 h) and no-response infants (median, 0.8 h; range, 0.5–2 h). There were no significant differences in antenatal, intrapartum or postnatal factors, except for dose of HC and the rate of HC-responsive infants between the groups (Tables 1, 2). CRH stimulation test and treatment course are given in Table 3. HC was effective in all CRH non-response infants. HC was effective, however, for only three CRH good-response infants, and additional dosage of catecholamine and/or vasopressin was needed in the other three cases. In all of the HC-responsive infants, blood pressure rose ≤1.5 h after HC treatment. Only one of the CRH good-response infants developed PVL. This PVL infant was an 816 g female infant born at a gestational age of 28 weeks 5 days. In this case of PVL, HC was not effective, and supplemental

**Table 1** Antenatal and intrapartum factors, CRH good response vs non-response in LCC, total (*n* = 16)

	CRH good response ( <i>n</i> = 6) Median (range) or <i>n</i> (%)	CRH non-response ( <i>n</i> = 10) Median (range) or <i>n</i> (%)	<i>P</i> -value
Gestational age	24 weeks 3 days (23 weeks 1 day–30 weeks 0 days)	24 weeks 3 days (23 weeks 1 day–30 weeks 2 days)	n.s.
Birthweight (g)	803 (595–1,126)	630 (577–1,318)	n.s.
Apgar score			
1 min	4.5 (1–8)	2.5 (1–7)	n.s.
5 min	6.5 (4–10)	3 (1–9)	n.s.
Male	4 (66.7)	7 (70.0)	n.s.
pH at birth	7.37 (7.27–7.45)	7.37 (7.23–7.41)	n.s.
Base excess at birth	−3.85 (−4.9 to 0.1)	−1.85 (−11.7 to 0.1)	n.s.
Hematocrit at birth (%)	37.5 (35–50)	32.6 (30.5–45)	n.s.
PROM	2 (33.3)	1 (10.0)	n.s.
Cesarean section	3 (50.0)	7 (70.0)	n.s.
SGA	1 (16.7)	1 (10.0)	n.s.
Multiple gestation	0 (0.0)	1 (10.0)	n.s.
Placental disruption	0 (0.0)	1 (10.0)	n.s.
Antenatal glucocorticoid	1 (16.7)	5 (50.0)	n.s.
CAM	1 (16.7)	4 (40.0)	n.s.

CAM, chorioamnionitis; CRH, corticotrophin-releasing hormone; LCC, late-onset circulatory collapse; PROM, preterm rupture of the membranes; SGA, small for gestational age (bodyweight <10th percentile for gestational age).

**Table 2** Postnatal factors, CRH good response vs non-response in LCC, total (*n* = 16)

	CRH good response ( <i>n</i> = 6) Median (range) or <i>n</i> (%)	CRH non-response ( <i>n</i> = 10) Median (range) or <i>n</i> (%)	<i>P</i> -value
Age at onset (days)	25 (14–64)	20.5 (6–56)	ns
Corrected GA at onset	31 weeks 0 days (27 weeks 5 days–33 weeks 1 day)	30 weeks 2 days (24 weeks 5 days–32 weeks 3 days)	ns
Duration of ventilation (days)	55.5 (0–116)	84 (0–148)	ns
Duration of oxygen (days)	277 (120–339)	288 (62–590)	ns
Surfactant	6 (100.0)	9 (90.0)	ns
Indomethacin	6 (100.0)	8 (80.0)	ns
RBC transfusion	4 (66.7)	9 (90.0)	ns
Erythropoietin	6 (100.0)	10 (100.0)	ns
TPN including lipid	6 (100.0)	10 (100.0)	ns
Iron treatment	6 (100.0)	10 (100.0)	ns
Glucocorticoid before onset	3 (50.0)	7 (70.0)	ns
CLD	6 (100.0)	10 (100.0)	ns
Apnea	6 (100.0)	10 (100.0)	ns
Methylxantine	2 (33.3)	0 (0.0)	ns
Caffeine	4 (66.7)	3 (30.0)	ns
ROP	3 (50.0)	7 (70.0)	ns
Diuretics	4 (66.7)	7 (70.0)	ns
Levothyroxine	0 (0.0)	0 (0.0)	ns
PVL	1 (16.7)	0 (0.0)	ns
Hydrocortisone dose (mg/kg)	8.5 (5–10)	5 (3.3–10)	<0.05
HC effective	3 (50.0)	10 (100.0)	<0.05

CLD, chronic lung disease; CRH, corticotrophin-releasing hormone; GA, gestational age; HC, hydrocortisone; LCC, late-onset circulatory collapse; PVL, periventricular leukomalacia; RBC, red blood cell; ROP, retinopathy of prematurity; TPN, total parenteral nutrition.

catecholamine and subsequent vasopressin were needed. It took 14.0 h to improve hypotension from the onset of LCC.

## Discussion

In this study, HC was effective in all cases of non-response to the CRH stimulation test. In contrast, HC was effective in only 50% cases of CRH good response, although the dose of HC was significantly higher than in the CRH non-response cases. Vasopressin

and/or catecholamine were needed in the CRH good-response infants for whom HC was not effective. This suggests that LCC has two different pathophysiologies, adrenal insufficiency and other causes, and this provides a clue to the treatment of LCC.

Late-onset circulatory collapse is defined as the acute onset of transient refractory hypotension and oliguria after the early neonatal period.<sup>1</sup> The underlying pathophysiology of LCC is considered to be relative adrenal insufficiency, which is well known in Japan, but not in North America or Europe.

**Table 3** CRH stimulation test results and LCC treatment course, total ( $n = 16$ )

Patient characteristics	CRH-stimulation test		Result	Treatment	Time from onset to BP recovery (h)
	Cortisol ( $\mu\text{g/dL}$ )				
	Before	After			
GA 24 weeks 3 days BW 638 g Male	9.2	9.4	Negative	HC 10 mg/kg	3.0
GA 23 weeks 3 days BW 622 g Male	5.9	7.1	Negative	HC 5 mg/kg	2.5
GA 30 weeks 0 days BW 1318 g Female	11.8	8.1	Negative	HC 5 mg/kg	3.0
GA 23 weeks 1 day BW 577 g Male	6.5	8.0	Negative	HC 5 mg/kg	2.0
GA 25 weeks 0 days BW 594 g Female	4.3	3.6	Negative	HC 5 mg/kg	2.5
GA 25 weeks 1 day BW 704 g Male	2.5	2.7	Negative	HC 5 mg/kg	2.5
GA 23 weeks 1 day BW 577 g Male	13.9	12.2	Negative	HC 3.3 mg/kg	3.0
GA 30 weeks 2 days BW 710 g Female	11.8	14.6	Negative	HC 5 mg/kg	2.0
GA 23 weeks 4 days BW 595 g Male	7	10.2	Negative	HC 5 mg/kg	3.0
GA 24 weeks 3 days BW 638 g Male	5.3	7.7	Negative	HC 7.1 mg/kg	1.5
GA 28 weeks 5 days BW 816 g Female <sup>†</sup>	9	13.5	Positive	HC 10 mg/kg→DOA(5 $\gamma$ )/DOB(5 $\gamma$ ), vasopressin (0.001 $\mu\text{g/kg/min}$ )	14.0
GA 23 weeks 3 days BW 622 g Male	6	15.9	Positive	HC 10 mg/kg→DOA(5 $\gamma$ )/DOB(5 $\gamma$ )	7.0
GA 28 weeks 3 days BW 961 g Female	7.5	52.0	Positive	HC 7 mg/kg→DOA(8 $\gamma$ )/DOB(8 $\gamma$ )	6.0
GA 28 weeks 1 day BW 1126 g Male	6.8	17.2	Positive	HC 5 mg/kg	4.1
GA 23 weeks 4 days BW 595 g Male	5.5	8.5	Positive	HC 5 mg/kg	4.0
GA 25 weeks 2 days BW 790 g Male	4.2	6.9	Positive	HC 10 mg/kg	4.5

<sup>†</sup>Developed periventricular leukomalacia. BP, blood pressure; BW, birthweight; CRH, corticotrophin-releasing hormone; DOA, dopamine; DOB, dobutamine; GA, gestational age; HC, hydrocortisone.

Transient adrenocortical insufficiency is most commonly reported in preterm infants of gestational age <30 weeks, and the majority of patients present in the first few days of life.<sup>3,4</sup> In Japan, LCC is considered to differ from transient adrenocortical insufficiency in early postnatal life.

Although most cases of LCC are transient, LCC may cause PVL.<sup>9–11</sup> Suzuki *et al.* suggested that PVL was associated

with LCC (OR, 2.57).<sup>11</sup> It is urgent that the pathophysiology of LCC be elucidated and the treatment established to improve hypotension immediately to prevent the onset of PVL. In this study, there was one infant who had PVL. In that case, the long time to improve hypotension compared with other non-PVL cases might lead to further PVL complications.

In this study, HC was defined as ineffective if blood pressure did not rise in the 2 h after treatment. Shimokaze *et al.* stated that median time from the initial HC dose to improvement was 4 h.<sup>10</sup> In all of the present HC-responsive infants, blood pressure rose  $\leq 1.5$  h after HC treatment. In addition, it is important to improve hypotension immediately in LCC, therefore we chose the 2 h cut-off accordingly. But the 2 h cut-off might be too early to judge the effectiveness of HC, and therefore the effectiveness of HC might have been underestimated.

Masumoto *et al.* reported that the serum cortisol concentration did not differ between infants with and without LCC, but the total serum concentration of precursors in the pathway to cortisol production was very high in infants with LCC.<sup>2</sup> They therefore suggested that it was not possible for preterm infants to synthesize sufficient cortisol for the degree of clinical stress when the requirement for cortisol was increased.<sup>2</sup> It is difficult, however, to evaluate adrenocortical function accurately on a one-point measurement. Therefore, CRH stimulation tests are performed to accurately evaluate adrenocortical function. Moreover, the strong point of this study is that the CRH stimulation tests were performed between LCC onset and HC replacement, with the patient in a critical condition.

Antenatal glucocorticoid use to prevent respiratory distress syndrome has increased. The efficacy of antenatal glucocorticoid is established, but they also have unfavorable effects. Niwa *et al.* suggested that infants exposed to antenatal glucocorticoid might have a lower response to CRH test at a postnatal gestational age of approximately 2 weeks.<sup>12</sup> In the present study, the onset of LCC in most cases was beyond a postnatal gestational age of 2 weeks. In addition, there was no significant difference in the rates of antenatal glucocorticoid between CRH good- and non-response infants, suggesting that the antenatal glucocorticoid was not associated with a lower response to CRH stimulation test.

Although catecholamine was used to treat HC-non-responsive infants, catecholamine is only a supplement to HC. We considered that most cases of LCC were induced by adrenal insufficiency. This study was planned to prove this hypothesis. For this reason, we selected HC without supplemental catecholamine for the first-line treatment in LCC. In the case of resistance to first-line treatment, supplemental catecholamine and subsequent vasopressin were considered. All CRH non-responsive infants responded to HC, thereby indirectly supporting the hypothesis. It is possible that some CRH-good response infants were sensitive to catecholamine prior to HC. This, however, does not disagree with the conclusion that negative CRH test is a predictor of HC effectiveness.

The pathophysiology of LCC without adrenal insufficiency remains unclear. Diuretics and levothyroxine have been suggested as the causes in some LCC cases.<sup>5,6</sup> In the present study, however, there were no significant differences in these treatments. LCC without adrenal insufficiency might be multifactorial. Early additional doses of HC might have been effective and vasopressin might be the first choice in CRH good response infants. HC was effective, however, even in 50% of

CRH good response infants. In addition, it takes a long time for the CRH stimulation results to be processed, and this might delay prompt treatment. We suggest that HC is therefore the first choice, but not vasopressin, even in CRH good response infants.

To the best of our knowledge, this is the first report to examine CRH stimulation tests in infants immediately following the occurrence of LCC. Although HC is the first-choice treatment for LCC, the CRH stimulation test might be useful for the second choice to stabilize circulation change immediately and prevent the onset of PVL. The CRH stimulation test was found to be effective for elucidation of the pathology and for selecting treatment in LCC.

The limitations of the present study are that it was retrospective and had a small sample size in a single institution. In addition, the dose of HC was not standardized. In the future, a prospective and multicenter study is essential to elucidate the pathophysiology of LCC after selection of the treatment protocol.

In this study, serum adrenocorticotrophic hormone (ACTH) was not measured because of the need to draw more blood. In addition, whether sufficient cortisol is secreted for the degree of clinical stress can be evaluated without measuring ACTH.

In conclusion, late-onset circulatory collapse has two different pathophysiologies: adrenal insufficiency and others. The CRH stimulation test might be useful for prompt treatment of LCC and prevention of PVL. These findings are useful for not only elucidating the pathology, but also for selecting treatment in LCC.

## Disclosure

The authors declare no conflict of interest.

## Author contributions

H.U. and Y.Y. designed the study. S.I., T.G., M.M., S.T., and T.K. collected and analyzed the data. H.U. and H.K. wrote the manuscript. All authors read and approved the final manuscript.

## References

- 1 Kawai M. Late-onset circulatory collapse of prematurity. *Pediatr. Int.* 2017; **59**: 391–6.
- 2 Masumoto K, Kusuda S, Aoyagi H *et al.* Comparison of serum cortisol concentration in preterm infants with or without late-onset circulatory collapse due to adrenal insufficiency of prematurity. *Pediatr. Res.* 2008; **63**: 686–90.
- 3 Ng PC. Adrenocortical insufficiency and refractory hypotension in preterm infants. *Arch. Dis. Child. Fetal Neonatal Ed.* 2016; **101**: F571–6.
- 4 Ng PC, Lee CH, Lam CW *et al.* Transient adrenocortical insufficiency of prematurity and systemic hypotension in very low birth weight infants. *Arch. Dis. Child. Fetal Neonatal Ed.* 2004; **89**: F119–126.
- 5 Kawai M, Kusuda S, Cho K *et al.* Nationwide surveillance of circulatory collapse associated with levothyroxine administration in very-low-birthweight infants in Japan. *Pediatr. Int.* 2012; **54**: 177–81.

- 6 Yagasaki H, Kobayashi K, Nemoto A *et al.* Late-onset circulatory dysfunction after thyroid hormone treatment in extremely low birth weight infant. *J. Pediatr. Endocrinol. Metab.* 2010; **23**: 153–8.
- 7 Fukuda S, Mizuno K, Kakita H *et al.* Late circulatory dysfunction and decreased cerebral blood flow volume in infants with periventricular leukomalacia. *Brain Dev.* 2008; **30**: 589–94.
- 8 Kobayashi S, Fujimoto S, Koyama N *et al.* Late-onset circulatory dysfunction of prematurity infants and late-onset periventricular leukomalacia. *Pediatr. Int.* 2008; **50**: 225–31.
- 9 Nakanishi H, Yamanaka S, Koriyama S *et al.* Clinical characterization and long-term prognosis of neurological development in preterm infants with late-onset circulatory collapse. *J. Perinatol.* 2010; **30**: 751–6.
- 10 Shimokaze T, Saito E, Akaba K. Increased incidence of late-onset circulatory collapse after changing clinical practice: A retrospective investigation of causative factors. *Am. J. Perinatol.* 2015; **32**: 1169–76.
- 11 Suzuki Y, Kono Y, Hayakawa T *et al.* Neonatal factors related to center variation in the incidence of late-onset circulatory collapse in extremely preterm infants. *PLoS ONE* 2018; **13**: e0198518.
- 12 Niwa F, Kawai M, Kanazawa H *et al.* Limited response to CRH stimulation tests at 2 weeks of age in preterm infants born at less than 30 weeks of gestational age. *Clin. Endocrinol.* 2013; **78**: 724–9.