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ORIGINAL RESEARCH

Clinical features of late-onset circulatory dysfunction in premature infants

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Background: Sudden unpredictable hypotension during the post-transitional period, termed late-onset circulatory dysfunction (LCD) of premature infants, has been reported in low birth-weight infants who overcame major problems during the early neonatal period. We investigated the clinical features of LCD and factors associated with the occurrence of LCD.

Methods: A multicenter retrospective case-control study. The clinical records of 1,004 children born at less than 32 weeks of gestation were reviewed. Patients with LCD were compared with age-matched non-LCD controls.

Results: Of the 1,004 infants, 73 (7.3%) were diagnosed with LCD, with the incidence differing significantly among institutions ($P<0.0001$). The median age of diagnosis was 16 days of age (range: 4–50 days) and 29 weeks of postmenstrual age (range: 25–35 weeks). The incidence of LCD was inversely correlated with gestational age at birth, except at 22 and 23 weeks. Compared with the control infants, the LCD infants had significantly higher incidences of birth by cesarean section (61/73 versus 48/73, $P<0.05$); hyponatremia (sodium <130 mEq/L) at the time of diagnosis (24/66 versus 3/39, $P<0.01$); deterioration of respiratory status within 24 hours before diagnosis (36/73 versus 6/73, $P<0.0001$); and periventricular leukomalacia (14/73 versus 4/73, $P<0.05$). Corticosteroids were effective in 52 infants who were unresponsive to volume expansion or inotropic agents. None of these infants died of LCD.

Conclusion: LCD is common but worthy of attention due to its association with periventricular leukomalacia. A review of institutional differences in treatment policies may contribute to the prevention of LCD.

Keywords: late-onset circulatory dysfunction of premature infants, low birth-weight infant, shock, adrenocortical insufficiency, periventricular leukomalacia

Introduction

Systemic hypotension frequently occurs in very low birth-weight infants during the early neonatal period.[1–4] During the post-transitional period, however, some of these infants experience sudden refractory hypotension that is usually resistant to volume expansion and inotrope treatment, a condition called late-onset circulatory dysfunction (LCD) of premature infants.[5–8] The onset of LCD is unpredictable, and it often occurs in the absence of obvious causes (such as hemorrhaging, sepsis, and symptomatic patent ductus arteriosus) in infants who overcame major respiratory and circulatory problems during the early neonatal period.

The number of infants with LCD has been increasing in Japan.[5–8] It was reported that the prevention of this disease could lead to improved neurological prognosis of those infants,[8] but the clinical features and pathogenesis of this condition have

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not yet been determined. So we performed a multi-center retrospective case-control study to investigate the clinical features of LCD and factors associated with its occurrence, and looked for clues to prevent this disease.

Methods

Study subjects

We reviewed the clinical records of all infants who were born at less than 32 weeks of gestation and were admitted to one of nine neonatal intensive care units in the Chubu area of Japan between January 1, 2000, and December 31, 2004. Infants who suffered early neonatal death, major anomalies, chromosomal abnormalities, or multiplets, except for dichorionic diamniotic twins, were excluded.

Study design

Each LCD infant was compared with gestational age matched (<1 week difference) non-LCD controls admitted to the same institution just after the LCD infant. Clinical data at and before the time of LCD diagnosis were compared with that of the control patient at the same age. Mean heart rate and blood glucose concentration measured on the day before LCD diagnosis, were compared with that of the control patient at the same day of age.

Definitions

LCD was defined as the sudden development, during the post-transitional period, of hypotension (20% decrease in systolic or mean blood pressure) and/or oliguria (50% decrease in urine volume or less than 1 mL/kg/hr of urine over 8 hours, or no urination for over 4 hours) after a period of stable respiration and circulation, without an obvious cause such as hemorrhaging, sepsis, or symptomatic patent ductus arteriosus. Symptomatic patent ductus arteriosus as a cause of hypotension was excluded by ultrasonography in all LCD patients. Each of these infants was assessed for C-reactive protein concentration and blood culture results, and only those negative for all these markers were confirmed as having LCD. Intraventricular hemorrhage was diagnosed by cranial ultrasonography.[9] Periventricular leukomalacia (PVL) was diagnosed by the presence of periventricular cysts (>3 mm) on cranial ultrasonography performed at 0, 1, 2, and 7 days of age, and once per week thereafter during hospitalization. In some infants, PVL was diagnosed by cranial computed tomography or magnetic resonance imaging after discharge from the hospital. In these infants, PVL was diagnosed by the presence of ventricular dilatation and/or reductions in periventricular white matter. Chorioamnionitis was defined as infection/inflammation of the membranes histologically diagnosed by pathologists at each hospital. Diagnoses of respiratory distress syndrome were based on clinical and chest radiographic findings.

Ethical approval

This study was approved by the ethics committee of Toyohashi Municipal Hospital, which waived the requirement for informed consent due to the retrospective nature of this study.

Statistical analysis

All statistical analyses were performed using JMP (Release 5.1.2; SAS Institute Inc., Cary, NC, USA). Differences between medians were analyzed using Wilcoxon rank-sum tests, and differences between means were analyzed using unpaired Student's *t*-tests. Categorical data were analyzed using the χ^2 test or Fisher's exact test. Variables with $P<0.2$ by bivariate analysis were included in multivariate analysis using logistic regression. A P-value <0.05 was defined as statistically significant.

Results

Incidence

Of the 1,236 infants born at less than 32 weeks of gestation, 232 were excluded, 40 due to early neonatal death, 15 for major anomalies, six for chromosomal abnormalities, 168 for being multiplets (not including dichorionic diamniotic twins), and three for loss of medical records. Of the remaining 1,004 infants, 73 (7.3%) were diagnosed with LCD, including 38/538 (7.1%) males and 35/466 (7.5%) females. In infants born at less than 28 weeks of gestation, the incidence was 14.8%. Incidence was inversely correlated with gestational age at birth, except at 22 and 23 weeks, and was highest at 24 weeks (14/58; 24.1%) (Figure 1). From 2000 to 2004, LCD tended to increase, being 6/166 (3.6%) in 2000, 15/208 (7.2%) in 2001, 10/196 (4.9%) in 2002, 17/211 (8.1%) in 2003, and 25/213 (11.7%) in 2004. The incidence of LCD differed significantly among the nine institutions ($P<0.0001$; Table 1).

Clinical features

Median age at the time of LCD diagnosis was 16 days of age (total range: 5–50 days) and 29 weeks 5 days of postmenstrual age (total range: 25 weeks 0 days to 35 weeks 2 days). We compared 73 LCD patients with 73 gestational age-matched controls. Table 2 shows the clinical characteristics of the two groups. There were no between-group differences in

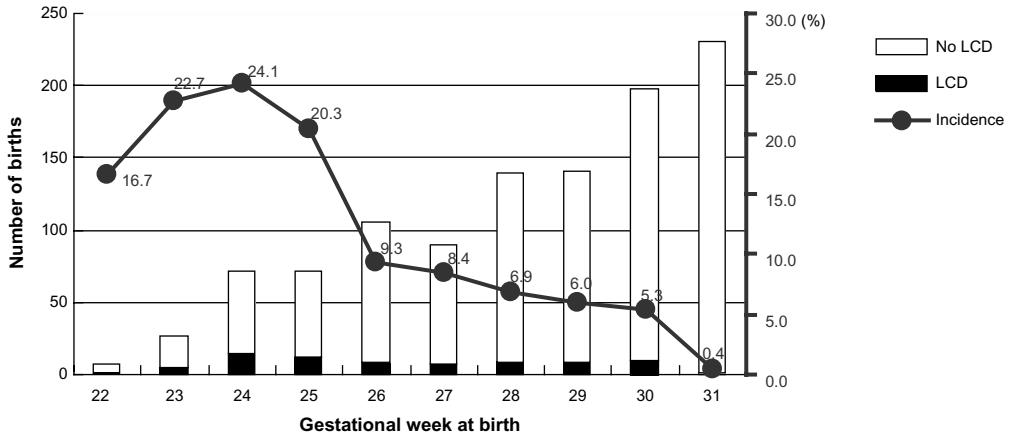

Figure 1 Relationship between incidence of LCD and gestational age at birth.
Note: The incidence of LCD was inversely correlated with gestational age at birth, except for at 22 and 23 weeks, and was highest at 24 weeks (14/58, 24.1%).

birth weight. Birth by cesarean section was statistically significantly more common in the LCD than in the control group (61/73 versus [vs] 48/73, P=0.013). The day before LCD diagnosis, mean ± standard deviation heart rate was higher in the LCD than in the control group (158.7±11.5 vs 151.9±10.3, P=0.0002). Moreover, the incidences of hyponatremia (Na <130 mEq/L, 24/66 vs 3/39, P=0.001) and hyperkalemia (K >5.5 mEq/L, 13/65 vs 2/39, P=0.037) were higher in the LCD group, as was the incidence of respiratory status deterioration within 24 hours before the diagnosis of LCD (36/73 vs 6/73, P<0.0001). At the time of LCD diagnosis, a higher percentage of infants in the LCD group required respiratory support (60/73 vs 44/73, P=0.0034), including continuous nasal positive airway pressure (24/73 vs 17/73, P=0.2), intermittent mandatory ventilation (16/73 vs 20/73, P=0.44), and/or high frequency oscillatory ventilation (20/73 vs 7/73, P=0.0056). Seven LCD infants, however, showed no signs of respiratory insufficiency and breathed spontaneously without oxygen supplementation. There were no between-group differences in the administration of prenatal steroids to mothers or postnatal steroids to infants during early neonatal period or in steroid inhalation at the time of LCD diagnosis. The frequency of steroid infusion after 7 days of age was statistically significantly higher in the LCD group in comparison with the non-LCD group (7/73 vs 1/73, P=0.027). The administration of diuretics (14/73 vs 5/73, P=0.027) and theophylline and/or caffeine (54/73 vs 45/73, P=0.011) at the time of diagnosis was statistically significantly more common in the LCD than in the control group.

Multivariate logistic regression analysis (Table 4) showed that deterioration of respiratory status within 24 hours before LCD diagnosis (odds ratio [95% confidence interval] 11.433 [3.87–40.56]; P<0.0001), cesarean section (odds ratio [95% confidence interval], 4.25 [1.30–15.60]; P=0.021), chorioamnionitis (odds ratio [95% confidence interval], 2.78 [1.08–7.59]; P=0.039), and PVL (odds ratio [95% confidence interval], 4.54 [1.14–21.93]; P=0.042) were significantly and independently associated with the onset of LCD.

Table 1 Incidence of LCD according to institution

Institution	Number of infants	Infants with LCD	Incidence (%)
A	203	36	17.7
B	208	16	7.7
C	138	7	5.1
D	127	1	0.8
E	85	2	2.4
F	109	0	0.0
G	48	10	20.8
H	29	1	3.4
I	57	0	0.0
Total	1,004	73	7.3

Notes: The incidence of LCD differed significantly among the 9 institutions (P<0.0001).
Abbreviation: LCD, late-onset circulatory dysfunction of premature infants.

Endocrinologic findings

In eleven LCD infants, adrenal function was investigated just prior to treatment. Table 3 shows plasma cortisol and adrenocorticotropic hormone concentrations in these infants.

Treatment

All LCD patients required some treatments. Of the 73 infants with LCD, 66 were treated with volume expansion, 65 were administered inotropic agents, and 52 were administered corticosteroids. Corticosteroids were effective in all 52 patients, including 51 who were unresponsive to volume expansion and/or inotropic agents. The numbers of patients in response to each regimen were as follows: two,

Table 2 Clinical characteristics of the LCD and control groups

Clinical features	LCD (n=73)	Control (n=73)	*P*
Birth-related factors			
Gestational age[#]	26 w 3 d (~24 w 4 d–28 w 6 d)	26 w 5 d (~25 w 1 d–29 w 2 d)	0.43
Birth weight (g)[#]	850 (~668.5–1,067)	852 (~728–1,100)	0.24
Outborn	1	6	0.12
C-section	61	48	0.013
Male:female	38:35	38:35	1
Light-for-date	14	12	0.67
APGAR score (1 minute)[#]	3 (~2–6)	4 (~2–7)	0.35
APGAR score (5 minutes)[#]	6 (~4–8)	7 (~5–9)	0.09
Chorioamnionitis	36/67	26/68	0.07
Clinical data on the day before LCD diagnosis			
Body weight/birth weight ratio	1.00±0.19	1.00±0.18	0.83
Water intake (mL/kg/day)	119.5±41.7	127.4±61.7	0.37
Heart rate (beats/min)	158.7±11.5	151.9±10.3	0.0002
Na <130 mEq/L	24/66	3/39	0.001
K >5.5 mEq/L	13/65	2/39	0.037
Blood glucose (mg/dL)	104.3±42.3	99.2±35.4	0.52
Respiratory status at LCD diagnosis			
Spontaneous respiration (room air)	7	12	0.22
Spontaneous respiration (O_2 supplementation)	6	17	0.0125
Respiratory support	60	44	0.0034
n-CPAP	24	17	0.2
IMV	16	20	0.44
HFOV	20	7	0.0056
Deterioration of respiratory status <24 hours before diagnosis	36	6	<0.0001
Medication			
Perinatal			
Prenatal steroid treatment	27	22	0.38
Postnatal steroid infusion before LCD diagnosis	13	9	0.35
<day 7	8	8	1.00
≧day 7	7	1	0.027
Indometacin for symptomatic PDA	15	22	0.18
At LCD diagnosis			
Diuretics	14	5	0.027
Theophylline and/or caffeine	54	45	0.011
Doxapram	10	15	0.27
Steroid inhalation	3	2	0.65
Oral Na supplementation	27	27	1
Complications			
Respiratory distress syndrome	56	51	0.349
Pulmonary hemorrhage	5	2	0.25
IVH (grade III and IV)	8	4	0.23
O_2 requirement (days)[#]	64 (~45–88.5)	61 (~26.5–79.5)	0.13
O_2 dependence at 28 days of age	66	54	0.009
O_2 dependence at 36 weeks of post conceptional age	36	28	0.21
PVL	14	4	0.012
ROP	33	23	0.1
Died	1	1	1

Notes: Data in the LCD at the time of LCD diagnosis were compared with data in the control group at the same age. [#], median (interquartile range).

Abbreviations: C-section, cesarean section; HFOV, high-frequency oscillatory ventilation; HOT, home oxygen therapy; IMV, intermittent mandatory ventilation; IVH, intraventricular hemorrhage; LCD, late-onset circulatory dysfunction of premature infants; n-CPAP, nasal continuous positive airway pressure; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; w, weeks; d, days.

volume expansion only; four, inotropic agents only; one, sodium loading only; one, corticosteroids only; 14, volume expansion + inotropic agents; four, volume expansion + corticosteroids; one, inotropic agents + corticosteroids; and 46, volume expansion + inotropic agents + corticosteroids.

Prognosis

The incidence of PVL (14/73 vs 4/73, *P*=0.012) was statistically significantly higher in the LCD than in the control group (Table 2). Of the 14 LCD infants with PVL, 13 were diagnosed with this condition more than 11 days after LCD

Table 3 ACTH and cortisol concentrations at LCD diagnosis

LCD	Age at LCD diagnosis (days)	Gestational age at birth	Birth weight (g)	ACTH (pg/mL)	Cortisol (μg/dL)
1	23	24 w 2 d	826	11	12.8
2	5	25 w 0 d	753	13.3	8.8
3	7	25 w 3 d	595	20.9	4.4
4	6	25 w 3 d	733	13.5	5.9
5	23	25 w 4 d	1,028	83	9.8
6	16	26 w 3 d	982	36.8	6.9
7	37	26 w 5 d	850	150	6.5
8	19	29 w 6 d	1,306	61	7.1
9	15	30 w 0 d	904	nd	5.4
10	10	30 w 5 d	1,352	35.6	5.1
11	5	30 w 6 d	1,130	63.3	5.6

Abbreviations: ACTH, adrenocorticotropic hormone; LCD, late-onset circulatory dysfunction of premature infants; nd, no data; w, weeks; d, days.

diagnosis (ie, more than 34 days after delivery), with the remaining infant diagnosed on the first day of life. Oxygen dependence was significantly higher in the LCD group at 28 days of age (66/73 vs 54/73, P=0.009) but was not at 36 weeks of postmenstrual age. None displayed any clinical symptoms and signs that suggested adrenal insufficiency without steroid administration after the recovery of LCD. One infant in each group died. The infant in the LCD group died of intestinal perforation at age 166 days, and the infant in the control group died of infection at age 27 days. None of the patients in either group died of LCD.

Discussion

Refractory hypotension resistant to volume expansion and vasopressors has been reported in a significant proportion of very low birth-weight infants during the early neonatal period.[4] Most of these patients respond to corticosteroids and show an inadequate adrenal response to stress, but this adrenal insufficiency has been reported to disappear by the end of the second week of life.[10] LCD can be clearly distinguished from hypotension during the early neonatal period by its occurrence during the post-transitional period, by a period of stable respiration and circulation preceding its diagnosis, and by its onset being sudden and lacking any obvious causes. An early report[11] described six extremely low birth-weight infants who suffered from glucocorticoid-responsive hypotension resistant to volume expansion and vasopressors, findings suggestive of LCD. In Japan, this condition was first recognized in 1996.[12] Since then, many LCD patients have been reported.[5,6,8]

We found that the incidence of LCD in infants born at less than 32 weeks of gestation was 7.3%. In Japan, LCD is

Table 4 Multivariate logistic regression analysis of clinical characteristics

Clinical features (outcome: LCD)	Regression coefficient	Odds ratio (95% CI)	P
Outborn	0.280	1.749 (0.075–18.152)	0.663
C-section	0.724	4.252 (1.301–15.597)	0.021
Gestational age at birth	0.195	5.973 (0.305–137.129)	0.247
Apgar score (5 minutes)	0.087	1.191 (0.450–3.166)	0.724
Chorioamnionitis	0.511	2.781 (1.075–7.592)	0.039
O_2 dependence at 28 days old	–0.170	0.711 (0.115–4.355)	0.711
Deterioration of respiratory status <24 hours before diagnosis	1.218	11.433 (3.871–40.559)	<0.0001
PVL	0.756	4.536 (1.137–21.927)	0.042
ROP	0.047	1.098 (0.396–3.015)	0.855
Postnatal steroid infusion before LCD diagnosis (≧day 7)	0.631	3.529 (0.355–83.760)	0.328
Respiratory support	0.597	3.298 (0.815–15.278)	0.105
Diuretics at onset	0.506	2.752 (0.722–11.949)	0.152
Theophylline or caffeine at onset	0.258	1.675 (0.646–4.490)	0.294

Abbreviations: C-section, cesarean section; CI, confidence interval; LCD, late-onset circulatory dysfunction of premature infants; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

common, and its incidence has recently increased. In spite of careful physical examination, we could not notice the onset of LCD in the majority of the patients. The oldest age of LCD onset was 35 weeks and 2 days of postmenstrual age. So we recommend that blood pressure and urine volume should be carefully monitored until 35 weeks of postmenstrual age.

The pathogenesis of LCD still remains unclear. Prematurity was found to affect the LCD onset. The incidence of LCD was inversely correlated with gestational age at birth, except for infants born at 22 and 23 weeks of gestation, in that the incidence of LCD in these infants was lower than that for infants born at 24 weeks of gestation. This may be related to the small numbers of patients born at 22 and 23 weeks (6 and 22, respectively) and their high mortality rates (63.6% and 35.7%, respectively). Improvement of the mortality of premature infants may be associated with a rise in the recent incidence of LCD.

It is interesting that high frequency oscillatory ventilation was associated with LCD. The reduction in venous return with this type of ventilation might contribute to LCD. Ultrasonography denied symptomatic patent ductus arteriosus in all the LCD patients at diagnosis and none was reported to show poor left ventricle motion. Thus, the high heart rate in the LCD group is suggestive of intravascular hypovolemia. But generalized dehydration does not seem to be a cause of LCD, as the ratio of body weight at diagnosis to birth weight did not differ between the LCD and control groups (Table 2). A previous report showed significant high body weight increase at diagnosis.[8] These findings suggest fluid shifts from the vessels to third spaces. In addition, diuretics, theophylline, and caffeine can contribute to intravascular hypovolemia.[13,14]

Cesarean section and chorioamnionitis were significantly associated with the onset of LCD, suggesting that some prenatal factors contribute to the pathogenesis of LCD. We reviewed the main reasons for cesarean section but could not find any differences between the LCD and non-LCD group.

LCD is responsive to corticosteroids, and some clinical features of LCD, including hypotension, hyponatremia, and hyperkalemia, resemble those of adrenocortical insufficiency. However, administration of hypotonic solution may induce hyponatremia, and renal failure induced by hypotension could result in hyperkalemia. The accurate evaluation of the adrenal function is necessary to conclude that LCD is adrenal insufficiency. The median plasma cortisol concentration in eleven LCD patients just prior to treatment (Table 3) was 6.5 μg/dL (interquartile range: 5.4–8.8 μg/dL), indicating a lack of stress despite hypotension.[19] It is very difficult to interpret these cortisol concentrations without knowing the degree of stress that these infants were experiencing at that time. We are sorry that adrenal function was not investigated in most of the patients because of the nature of the retrospective study. Infants who have received steroids should be carefully examined, for some of them might develop adrenal insufficiency secondary to the exogenous steroid. Of the 73 LCD patients, 18 were administered steroids during the postnatal period before LCD diagnosis. We could classify postnatal steroids treatment into two categories. The first category was the administration for hypotension during the early neonatal period (<day 7), and the other one was the infusion for respiratory distress thereafter (≥day 7). The frequency of steroid administration during the early neonatal period was not different between the LCD and non-LCD groups (8/73 vs 8/73). On the other hand, the frequency of steroid infusion after 7 days of age was significantly higher in the LCD group (7/73 vs 1/73: P=0.027). There is a possibility that the adrenal cortex suppression caused by steroid administration contributes to the onset of LCD in those patients. However, most of the LCD patients (66/73) developed the disease without steroid infusion after 7 days old. We are convinced that some factors other than postnatal steroid infusion affect the onset of LCD. The total concentrations of cortisol precursors were reported to be statistically significantly higher in those patients than in age matched controls,[15] suggesting that this circulatory dysfunction is caused by a limited ability to synthesize sufficient amounts of cortisol relative to the degree of clinical stress. In contrast, the hypothalamic–adrenal axis was found to be intact in one patient (patient E),[11] suggesting that factors other than adrenal insufficiency contribute to the development of LCD. We should be careful about concluding that LCD is adrenal insufficiency. Further investigations of adrenal function, including the response of the hypothalamic–pituitary–adrenal axis to stress, are necessary to clarify the pathogenesis of LCD.

Multivariate logistic regression analysis revealed that PVL was statistically significantly associated with LCD. PVL associated with LCD was characterized by late-onset. The onset of cystic lesions in the PVL infants of the LCD group occurred in all but one patient more than 34 days after delivery, later than reported previously.[16,17] Stratification of patients with PVL into those with early-onset (at ≤28 days of age) and late-onset (at >28 days of age) PVL showed that LCD was significantly and independently associated with late-onset PVL.[7] In most infants with LCD, systemic hypotension continued for more than several hours. We speculate that systemic hypotension for such a long time may adversely affect brain perfusion and contribute to the development of

PVL. Indeed, of the 14 infants with PVL in the LCD group, 13 were diagnosed more than 11 days after LCD diagnosis. However, clinical relevance of this association is limited. The age of PVL diagnosis greatly varied among the patients. Thus various other factors during the period before PVL diagnosis may be responsible for the development of PVL. Intrauterine infection–inflammation and cytokine release are also thought to contribute to PVL.[16,18] The incidence of chorioamnionitis was similar in LCD infants with (5/14) and without (31/53) PVL, suggesting that intrauterine infection–inflammation did not contribute to PVL in these LCD infants.

Our report is the first multi-center analysis of LCD and revealed that the incidence of LCD varied widely among institutions, from 0% to 20.8%. The difference of the patient's prematurity among participating centers may influence the incidence of LCD. So we investigated the correlation of LCD incidence and the mean gestational age of study infants in each institution, but no correlation was found. Although we used the same definition for LCD through all our institutions, the ascertainment bias due to the differences in monitoring by institutions and by years may affect the incidence of LCD. Institutional differences in treatment policies, including fluid and electrolyte administration, indications for diuretics, ventilator settings, and temperature control may also influence the LCD onset. Unfortunately we could not obtain enough data for statistical analyses of these issues because of the nature of the retrospective case-control study. A review of the differences in institutional treatment policies, in larger-scale prospective trials, may identify strategies to prevent LCD.

Disclosure

The authors report no conflicts of interest in this work.

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